University of Alberta

MODULATION OF VENTILATORY MECHANICS DURING EXERCISE IN VENTILATION-LIMITED POPULATIONS

by

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A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Medicine
Faculty of Physical Education and Recreation

Edmonton, Alberta
Fall 2007

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Your file Votre référence
ISBN: 978-0-494-32929-0
Our file Notre référence
ISBN: 978-0-494-32929-0

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ABSTRACT

The aim of this thesis was to examine the impact of modifications to ventilatory constraint in populations who have reductions in expiratory flow and ventilatory limitations during exercise. The first study examined the effect of the self-contained breathing apparatus (SCBA) regulator on work of breathing (WOB) and lung volume changes in healthy subjects. The second study further examined the effect of the SCBA on the above outcomes and on pulmonary function and respiratory muscle fatigue during stair-stepping (healthy subjects). In addition, the effect of breathing heliox on the above variables was studied. The third thesis study examined the effect of heliox on ventilatory constraint, exercise tolerance, and leg muscle fatigue in patients with chronic obstructive pulmonary disease (COPD).

The main results of the first study were that, compared to a low resistance breathing valve (RV), the SCBA regulator increased inspiratory elastic (32%), expiratory resistive (59%), and total WOB (13%), and increased end-expiratory lung volume creating a plateau in end-inspiratory lung volume at approximately 90% of vital capacity. When the above variables were examined with the full SCBA and compared to the RV in the second study, similar results were found. In addition, resting pulmonary function was reduced with the SCBA. Exercise with the SCBA induced reductions in both inspiratory and expiratory maximal pressures indicating the presence of respiratory muscle fatigue. When compressed air was replaced with heliox in the SCBA, end-expiratory lung volume, total WOB, and respiratory muscle fatigue were reduced. These observations regarding the effect of heliox on ventilatory function led to the third study, which found that heliox increased exercise tolerance (53%) and leg muscle fatigue (15%) in patients with COPD, but only in those limited by ventilatory constraints who did not have a significant level of leg fatigue while breathing room air. Those patients who did have leg fatigue on room air did not increase exercise tolerance despite reduced ventilatory constraint. Together the findings of this research indicate that reducing ventilatory constraint during exercise can have

specific positive effects on exercise performance in populations who are ventilatory limited and have implications for occupational or rehabilitation exercise training.

This thesis is dedicated to my wife, Melanie, and my son, Braeden, who was born the very day I started my final thesis research project and inspired me to complete this thesis quickly.

ACKNOWLEDGEMENTS

I would like to acknowledge the contribution of several people that, without whom, this thesis would not have been possible, and without whom I would not be the researcher I am today. First, Dr. Richard Jones, my home department supervisor, is the consummate inventor. Dick is both well respected internationally and humble enough that he is loved by his students and colleagues. Dick is the type of academic who I attempt to model myself after – he is hard-working, clever, and inventive, but also a highly respected teacher and mentor. Dick's contributions to my research and to my development as both an academic and a person are impossible to describe with words. I am proud to say that everything I know about respiratory physiology (and much about life), I learned from Dick.

Second, but not less important, Dr. Stewart Petersen, my co-supervisor, is the ultimate hands-on scholar. Stu's passion for exercise and work physiology is exemplified by his desire to be the first test subject in all of his students' exercise studies. I am constantly amazed and inspired by Stu's dedication to his students and colleagues in providing a research environment that is second to none. Stu's approach to problem solving has really encouraged me to think beyond the 'little black box'. And, despite his obvious fault of being a die-hard Eskimos fan, he has truly become a friend and a colleague with whom I hope to continue working for many years.

Third, Dr. Mark Haykowsky, the final member of my supervising committee, is the adventurous physiologist. Mark's no-nonsense approach to cardiopulmonary physiology has been like a breath of fresh air. I have particularly enjoyed, and benefited from, our discussions about chronic disease rehabilitation and about the importance of considering heart-lung interactions during exercise in patient populations.

Fourth, I would like to acknowledge the valued and expert participation of my examining committee Dr. David Collins and Dr. Robert Haennel, and my external examiner, Dr. Francois Maltais. All three of these knowledgeable and professional scholars helped make my thesis defense a pleasurable experience, when it certainly could have been otherwise.

Fifth, the contribution of my research collaborators has been exceptional. I am fortunate to have had enthusiastic and creative individuals with which to work. I acknowledge the contributions of

Dr. Neil Eves, Jonathan Mayne, Timothy Hartley, Dr. David Collins, Olle Lagerquist, Dr. Darcy Marciniuk, and Michal Pasiorowski.

Last, but certainly not least, I acknowledge the tireless and enthusiastic participation of my research subjects. Between having catheters inserted in their noses, exercising to exhaustion in unbearable heat, having their muscles shocked, and having to tolerate my dry sense of humour, it's a wonder I was able to recruit such excellent subjects. Thank you all!

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LIST OF ABBREVIATIONS

ATS	American Thoracic Society
BA	self-contained breathing apparatus exercise condition
BA-A	self-contained breathing apparatus with compressed air
BA-H	self-contained breathing apparatus with heliox
BW	body weight
C_{CW}	chest wall compliance
C_L	lung compliance
COPD	chronic obstructive pulmonary disease
DH	dynamic hyperinflation
D_LCO	diffusion capacity of the lung for carbon monoxide
ECG	electrocardiography
EELV	end-expiratory lung volume
EFL	expiratory flow limitation
EILV	end-inspiratory lung volume
EMG	electromyography
F	fatiguers
FEF_{50}	forced expiratory flow rate at 50% vital capacity
FEV_1	forced expiratory volume in one second
FI	fatigue index
FPE	fire protective equipment
FRC	functional residual capacity
FVC	forced vital capacity
GXT	graded exercise test
HE	heliox
He	helium
HR	heart rate
IC	inspiratory capacity
IRV	inspiratory reserve volume
ISO	isotime exercise condition
ITT	interpolated twitch technique
MEP	maximal expiratory pressure
MIP	maximal inspiratory pressure
MVIC	maximal voluntary isometric contraction

MVV	maximal voluntary ventilation
NF	non-fatiguers
O_2	oxygen
P,pe	peak expiratory pressure
P,pi	peak inspiratory pressure
P,sw	pressure swing
PEF	peak expiratory flow rate
Pes	esophageal pressure
Pm	mask pressure
PO	power output
RA	room air exercise condition
RR	respiratory rate
RV	Rudolph valve (low resistance breathing valve) exercise condition
SCBA	self-contained breathing apparatus
S_PO_2	oxygen saturation by pulse oximetry
SR	step rate
T_C	core temperature
T_I/T_{TOT}	duty cycle
TLC	total lung capacity
T_WVL	vastus lateralis twitch torque
$\dot{V}$	flow rate
VA	voluntary activation
VC	vital capacity
VCO_2	carbon dioxide production
V_E	minute ventilation
VO_2	oxygen consumption
V_T	tidal volume
WOB	work of breathing
WR	work rate

CHAPTER ONE
SCIENTIFIC FRAMEWORK

1.1 INTRODUCTION

Understanding the mechanisms of an individual's exercise limitation is crucial for the clinical exercise physiologist or the rehabilitation professional. Typically, the cardiovascular system is thought to be the primary limiting factor during high intensity endurance performance – for good reason. Most healthy populations are limited aerobically by the ability of the heart to increase stroke volume, and consequently, cardiac output (Bassett and Howley, 2000). During maximal exercise, the attainment of a maximal cardiac output limits oxygen delivery and blood flow, which, among other factors (see section 1.4.2), leads to the development of muscle fatigue and exercise cessation (Cole and Brown, 2000; Hogan et al, 1998). In the average person, the lung is 'overbuilt' and is not a primary cause of exercise limitation (Dempsey, 1986). There are several situations, however, where the response of the ventilatory system is inadequate to meet the gas exchange demands of heavy exercise and may be a primary factor limiting exercise. A ventilatory limitation during exercise can occur due to deficiencies in ventilatory or airflow mechanics, alterations in lung and chest wall compliance, increased airflow resistance, increased respiratory muscle work or any combination of the above (Johnson et al., 1999; Dempsey, 1986).

The research conducted for this thesis was designed to explore the pulmonary physiology related to the nature of ventilatory limitations during heavy exercise and to examine the impact of modifying ventilatory capacity on selected aspects of exercise performance, including work of breathing and peripheral muscle fatigue, in healthy subjects wearing a self-contained breathing apparatus (SCBA) and in patients with chronic obstructive pulmonary disease (COPD). The first study (Chapter 2) examined the effect of the SCBA regulator on ventilatory mechanics and work of breathing during cycling exercise. The second study (Chapter 3) examined the effect of the SCBA regulator on pulmonary function, ventilatory mechanics, work of breathing, and respiratory muscle fatigue during stepping exercise. The third study (Chapter 4) examined the effects of inhaling heliox during cycling exercise on endurance and peripheral muscle fatigue in patients with COPD. In addition to the main research completed for this thesis, three papers are presented as appendices representing some of the supplementary work completed during the course of this thesis research. The first is a review article (Appendix B) examining the impact of intensity of training in patients with COPD and how an understanding of the exercise limitations can lead to better exercise prescription. The second is a research study (Appendix C) which is an example of how the methods developed for this thesis research can be applied to the evaluation of clinical treatment methods in respiratory disease. The third is a research study (Appendix D) in which the effects of breathing 70% helium and 30% oxygen on the six minute walk distance in patients with COPD was investigated. As well, the published print version of the research conducted for Chapter 2 is presented in Appendix E. This introductory chapter will examine the pertinent literature that led to the completion of the thesis research and will conclude with statements of purpose and hypotheses of each of the three thesis studies.

1.2 VENTILATORY MECHANICS AND EXERCISE LIMITATION

Increases in alveolar ventilation during exercise are achieved by increases in both tidal volume and respiratory rate. Typically, tidal volume increases early during incremental exercise followed by a more rapid rise in respiratory rate at higher exercise intensities (ATS / ACCP, 2003). The increased tidal volume is achieved by active inspiratory muscle activity to increase end-inspiratory lung volume (EILV) and by a combination of passive lung recoil and expiratory muscle activity to decrease end-expiratory lung volume (EELV) below functional residual capacity (FRC). The decrease in EELV during exercise is an important compensatory mechanism to maintain lower levels of inspiratory muscle work (Roussos and Campbell, 1986). As both lung and chest wall compliance decrease as lung volume increases, a given change in tidal volume at higher lung volumes will result in a greater level of inspiratory elastic work of breathing for the same tidal volume change at lower lung volumes. As well, the decrease in EELV aids inspiration by optimizing diaphragm length and allowing the outward recoil of the chest wall to assist in overcoming part of the inspiratory resistive work (Henke et al, 1988). The lower EELV, however, increases expiratory airflow resistance and raises the risk that exercise expiratory flow encroaches upon the maximal expiratory flow-volume envelope (expiratory flow limitation; EFL) (Pellegrino et al, 1993). In healthy younger individuals with an average fitness level, however, EFL is not usually present and a decrease in EELV is achieved without adverse consequences (Johnson et al, 1992). The ventilation required for a given level of exercise may be constrained or the work of breathing increased, however, if expiratory resistance is increased or an EFL is present (McClaran et al, 1999) as presented in sections 1.2.1 and 1.2.2. As well, the degree of ventilatory limitation can be modified and delayed through the use of heliox as presented in section 1.2.3.

1.2.1 Ventilatory constraint

Ventilatory limitation during exercise occurs when the ventilatory requirement reaches ventilatory capacity during exercise. This limitation can be expressed as a decrease in ventilatory capacity, an increase in ventilatory demand, or both (See appendix B; Butcher and Jones, 2006; O'Donnell, 2001). Although increases in ventilatory requirement for a given level of exercise are a consequence of many disease states, it is the decreased ventilatory capacity that is the hallmark of respiratory disease and is primarily responsible for the ventilatory constraint (O'Donnell, 2001). Therefore, the focus of this thesis research was to examine the impact of the ventilatory constraint and not the ventilatory requirement associated with exercise limitation.

The traditional view of ventilatory constraint during exercise in clinical populations relates the peak exercise ventilation (V_{Epeak}) rate to a measured or predicted maximal voluntary ventilation (MVV) rate (Johnson et al, 1999). Thereby, if V_{Epeak} reaches or exceeds MVV, a ventilatory limitation due to ventilatory constraint occurs. Several limitations to the use of MVV as an indicator of ventilatory capacity have been expressed (Johnson et al, 1999). For example, the pattern of breathing during an MVV maneuver is markedly different than that which occurs during maximal exercise (Johnson et al, 1999). Subjects performing an MVV maneuver tend to exhibit a decreased tidal volume and increased respiratory rate compared to that obtained during maximal exercise. Most conclusively, however, the fact that patients with lung disease often achieve a V_E/MMV of greater than 100% indicates that MVV does not adequately represent the maximal ventilation possible (ATS/ACCP, 2003).

Perhaps a better indicator of ventilatory constraint is the inspiratory capacity (IC). IC maneuvers are a valid and reliable method of tracking the changes in EELV during exercise (IC) (Babb and Rodarde, 1991; Yan et al, 1997b) and represent the maximal operating limits of tidal volume expansion for a given level of exercise (O'Donnell et al, 2001) if a limitation to the normal decrease in EELV is present (such as an EFL). Once EELV is estimated by IC, the addition of tidal volume (V_T) will estimate EILV (EELV + V_T = EILV). If the IC is compared with tidal volume during exercise (V_T/IC) an index of the relative limitation on tidal volume expansion is obtained (O'Donnell et al, 2001). This index also reflects the inspiratory reserve volume (IRV) or the degree that EILV approaches total lung capacity (TLC). A V_T/IC approaching 100% would indicate that the tidal volume required to reach a certain level of ventilation is close to reaching both the upper (IRV) and lower (IC) limits of expansion.

As mentioned previously, in healthy individuals with average fitness levels, ventilatory constraint is not usually a concern. There are certain populations, however, where this is not so. Any abnormality that constrains tidal volume or breathing frequency has the potential to result in ventilatory constraint. Examples would include patients with chest wall disease or interstitial lung disease where tidal volume is constrained or patients with airway obstruction where both tidal volume and breathing frequency are constrained. I will not address tidal volume constraint due to chest wall or interstitial lung disease in this thesis and the focus will be on situations where the resistance to expiration is increased. More specifically, ventilatory constraint is common in situations where either a significantly increased expiratory resistance or an EFL are present (McClaran et al, 1999) and cause an increase in lung volumes for a given level of ventilation. In the case of an EFL, reductions in the ability to increase expiratory flow rates during exercise initially cause an increased expiratory time to maintain the normal EELV response during exercise. When ventilation and flow rates increase, however, the higher degree of EFL causes expiration to cease prior to attaining the desired EELV and, therefore, EELV increases (McClaran et al, 1999). If EELV increases to or beyond FRC, dynamic lung hyperinflation (DH) is said to have occurred. As EELV during DH increases, IC decreases and the V_T/IC ratio progresses toward 100%. DH due to EFL is considered the primary cause of the ventilatory limitation observed in patients with COPD as will be discussed in section 1.4.1. As well, DH has been observed during heavy exercise in healthy older subjects (Johnson et al, 1991), healthy females (McClaran et al, 1998), and in elite endurance athletes (Johnson et al, 1992) due to EFL. EFL, however, is not required to observe decreases in IC. McClaran and colleagues (1999) demonstrated that even an impending EFL or an increased expiratory resistance can also cause an increase in lung volumes during exercise. It may be that the increased expiratory pressure required to increase flow rates in the presence of increased expiratory resistance is intolerable, however, this hypothesis has not been directly explored to my knowledge. Certainly, the sensation of dyspnea is increased with greater expiratory resistance (Iandelli et al, 2002); however, whether this directly translates to a change in the EELV response during exercise remains to be determined. There are several consequences associated with increases in ventilatory constraint including a reduced maximal ventilation (McClaran et al, 1999), reduced cardiac output (Stark-Leyva et al, 2004) and increased dyspnea for a given work rate (Iandelli et al, 2002). Most notably, however, is the increased work of breathing associated with both the increased expiratory resistance and the resultant DH.

1.2.2 Work of breathing

The work of breathing (WOB) can also be viewed as a potential independent limitation on ventilatory capacity during very heavy exercise. Respiratory muscle work requires higher oxygen consumption merely to achieve the appropriate ventilation rate for a given level of exercise (Aaron et al, 1992b). During incremental exercise, there may be a "critical ventilation" whereby the oxygen cost of ventilation is so high that further increases in ventilatory rate would require all of the extra oxygen consumption to be devoted to the respiratory muscles, leaving no potential to increase oxygen delivery to the other exercising muscles (Otis et al, 1950). This critical ventilation does not normally occur in healthy subjects with average fitness levels where the oxygen cost of ventilation at maximal exercise reaches only 10 – 15% of total body oxygen consumption (Aaron et al, 1992b). Critical ventilation, however, may occur in individuals with higher levels of fitness, particularly females (Aaron et al, 1992b), or in patients with COPD (Levison and Cherniak, 1968) where the increased work of breathing for a given exercise work rate is a higher proportion of total energy expenditure (up to 40% of total body oxygen consumption in patients with COPD; Levison and Cherniak, 1968).

Despite the lack of a critical ventilation in the average individual, the work of breathing achieved during heavy to maximal exercise has been shown to have a significant negative impact on cardiac output (Harms et al, 1998), leg muscle blood flow (Harms et al, 1997), leg muscle fatigue (Romer et al, 2006) and ultimately exercise ventilation and performance (Harms et al, 2000). Of particular interest to the work in this thesis, is the relationship between work of breathing and leg muscle fatigue. In healthy fit subjects, increasing the work of breathing with inspiratory resistors significantly increases leg muscle contractile fatigue, presumably through a decrease in leg muscle blood flow (Romer et al, 2006) mediated through sympathetic vasoconstriction usually in the presence of respiratory muscle fatigue (Dempsey et al, 2002). Increased WOB during exercise predisposes the respiratory muscles to the development of muscle fatigue (Babcock et al, 1995), which drive the changes in limb vascular resistance, leg blood flow (Derchak et al, 2002; Sheel et al, 2001), maximal ventilation, and exercise performance (Dempsey et al, 2002) causing a ventilatory limitation. Although the research conducted for this thesis did not assess the cardiovascular effects of changes in WOB, an understanding of the consequences of increased WOB on exercise performance is essential in interpreting the results. Rather, Chapters 2 and 3 will focus more on the measurement and determination of WOB in the presence of ventilatory limitations than on the overall effects of WOB on exercise performance.

WOB can be defined as the integrated area of the change in respiratory muscle pressure over the change in lung volume (Roussos and Campbell, 1986). One of the more common methods of determining WOB is by plotting changes in respiratory muscle pressure (as estimated by esophageal pressure) with changes in lung volume during a single breath to create a pressure-volume loop (Campbell diagram) (Roussos and Campbell, 1986). In many studies, the WOB is the integrated area within the entire loop and assumed to be the total work done on the lung (Aaron et al, 1992a; Harms et al, 1998; for example). There are a few concerns with this method, however. First, the pressure-volume loop reflects a combination of inspiratory and expiratory work, however, measurement of the total integrated area cannot determine the relative contributions of the work to inspire or expire (Roussos and Campbell, 1986). Second, without adequate knowledge of the relationship between the tidal pressure-volume loop and the lung and chest wall compliance curves, the area within the loop will not reflect the relative components of elastic and resistive work (Sliwinski et al, 1998). Third, there is a significant amount of elastic work performed that falls outside of the pressure-volume loop and is not accounted for (Roussos and Campbell, 1986). Fourth, because EELV falls below FRC and EILV rises above the relaxation volume of the chest wall during exercise, some of the elastic work will be done against the recoil of the chest wall and not just the lung (Roussos and Campbell, 1986). In a true representation of a Campbell diagram, the tidal pressure-volume loop is plotted on the measured or estimated lung and chest wall compliance curves and a more accurate determination of the total WOB (and its components of inspiratory elastic, inspiratory resistive, expiratory elastic, and expiratory resistive work) can be measured. This technique likely still underestimates the actual total WOB incurred during exercise. The Campbell diagram does not account for the work done to overcome the inertial or flow resistive components of the chest wall (Roussos and Campbell, 1986), nor does it account for changes in chest wall compliance due to rib cage deformation during heavy exercise (Aaron et al, 1992). For more details on the methodology of measuring WOB, see Chapters 2 and 3.

1.2.3 Heliox

Inhalation of helium-based gas mixtures such as heliox has been used clinically and in research for over 70 years as a method of altering ventilatory mechanics by reducing respiratory resistance (since Barach 1934; 1936). Heliox is a normoxic gas that uses helium as the inert gas instead of nitrogen (21% O_2, 79% Helium; He). Helium has a density approximately 7 times lower than that of nitrogen with only a very slight increase (8%) in viscosity (Esposito and Ferretti, 1997). Therefore, heliox has a total gas density of approximately one third that of normal air with a viscosity of only 1.1 times greater than air (Brice and Welch, 1983) and has a significant effect on airflow and flow resistance. For a normal person during air breathing at lower flow rates, mass airflow is laminar and has a relatively low flow resistance. As flow rates increase during exercise, airflow transitions to turbulent flow with a higher flow-resistance at a Reynold's number of approximately 2000 (Brice and Welch, 1983). Reynold's number is proportional to the product of airway diameter, flow rate, and gas density divided by gas viscosity (Murphy et al, 1969). Therefore, for a given airway diameter and lung volume, heliox increases gas flow rate at any Reynold's number, increases the flow rate at which the transition from laminar to turbulent flow occurs, and reduces the flow resistance even once turbulent flow occurs (Esposito and Ferretti, 1997). As such, it would be expected that heliox would have a significant effect on both of the above ventilatory limitations during exercise; however, this phenomenon has not been studied extensively.

A consistent finding with heliox breathing, compared to air breathing, is an increase in the maximal flow volume envelope during spirometry, particularly during a large part of the forced expired maneuver (Schilder et al, 1963) as demonstrated in Chapter 3, Figure 3-2. At high lung volumes, where flow resistance is greatest in the larger airways, airflow is primarily turbulent and most susceptible to reductions in gas density with heliox (Gelb and Klein, 1977). As lung volume decreases, the greatest flow resistance shifts to the smaller, more peripheral airways where airflow is primarily laminar. The point where heliox no longer exerts a positive effect on maximal expiratory flows, and the room air and heliox expiratory flow curves meet, is called the volume of isoflow (Gelb and Klein, 1977). At the volume of isoflow and below, flow rates may actual reduce because laminar airflow is more susceptible to the slight increase in gas viscosity with heliox (Schilder et al, 1963). In healthy subjects, the portion of the expired flow volume loop that is typically used during exercise is above the volume of isoflow and is affected by the flow-enhancing properties of heliox (Babb, 1997). The effect of the increased maximal flow-volume relationship is the potential to generate greater exercise flow rates and to reduce the potential for EFL (McClaran et al, 1998; Palange et al, 2004). The effect on the control of EELV, however, is quite variable in healthy subjects and not always dependent on the presence of EFL (Babb, 1997). In healthy exercising humans, heliox breathing has been shown to have either no effect on EELV (Henke et al, 1988) or to decrease EELV (Babb, 1997). The effect of heliox on lung volumes and ventilatory constraint in patients with exercise EFL, however, is much clearer; as will be presented in section 1.4.3.

Despite the clear benefit of heliox on respiratory resistance and flow (Esposito and Ferretti, 1997), its effects on WOB are less clear and more variable. Heliox breathing has been shown to decrease resting (Gainnier et al, 2003) and short-term WOB during submaximal, moderate intensity exercise (Eves et al, 2006) in patients with COPD, but to have no effect during exercise in healthy younger (Babb 1997) or older (Babb et al, 2003) subjects or in patients with mild airway obstruction (Babb, 2001). The studies that have shown no change in WOB, however, do show an increase in minute ventilation such that the WOB for a given ventilation rate appears to be lower (Babb, 1997). It is unclear as to the type of subjects or test conditions by which heliox will decrease total work of breathing; however, it appears that the flow resistive unloading effects may be offset if a relative hyperventilation occurs (Babb and DeLorey, 2002).

Along with the variability observed in studies examining the effects of heliox on measures of ventilatory capacity there is the lack of consensus regarding changes in exercise tolerance in healthy subjects. Studies have shown either no change (Babb et al, 2003; Babb 2001;1997; Esposito and Ferretti, 1997) or an increase (Powers et al, 1986) in maximal oxygen consumption (VO_{2max}). Heliox appears to increase time to exhaustion during high intensity exercise more consistently (Tong et al, 2004; Powers et al, 1986; Wilson and Welch, 1980; Brice and Welch, 1983). Perhaps the lack of consistency in determining the effect of heliox on exercise tolerance is related to whether or not a ventilatory limitation occurred in each subject. It might be expected that subjects with ventilatory limitation during exercise would respond to the unloading effects of heliox by increasing exercise tolerance, whereas those who do not have ventilatory limitation would not. This premise has implications for the use of heliox in the two study populations used for this study. The effects of heliox breathing with the SCBA and in COPD will be presented in sections 1.3.3 and 1.4.2, respectively.

1.3 THE SELF-CONTAINED BREATHING APPARATUS

1.3.1 Effects on exercise and work tolerance

The SCBA is essential equipment for firefighters and other occupations to prevent inhalation of harmful gases or fumes during work in noxious environments. It has been well established, however, that the SCBA has a significant negative influence on exercise tolerance. Raven et al. (1977) and Louhevaara et al. (1986) found that the SCBA reduces maximal exercise capacity by 20 and 17%, respectively. SCBA technology has changed significantly since their work, but more recent research using modern technology has demonstrated similar findings. Dreger et al (2006) demonstrated a 17% reduction in VO_{2max} that was explained mostly by a reduction in peak exercise ventilation (r = 0.81). Eves et al (2005) found a 15% reduction in VO$_{2max}$ using a similar SCBA but also found that the regulator component accounted for most of reduced VO$_{2max}$. These findings combined indicate that the SCBA imposes a ventilatory limitation during heavy exercise that can be primarily attributed to the SCBA regulator. The exact mechanisms of this regulator-induced ventilatory limitation have not been determined; however, examining the effects of the SCBA on ventilatory function can provide some direction.

1.3.2 Effects on ventilatory function

Associated with the findings of a ventilatory limitation with the SCBA are specific effects on ventilatory function. The SCBA reduces peak exercise ventilation rate with an attenuated tidal volume but no significant change in respiratory frequency (Dreger et al, 2006; Eves et al, 2005). Despite no difference in total respiratory cycle time, the duty cycle (inspiratory time: total time per breath) is significantly reduced with the SCBA, indicating that a greater expiratory time is required to achieve a given level of ventilation (Eves et al, 2005). As well, the SCBA reduces peak exercise expiratory flow and increases the expiratory mask pressure and external expiratory resistance at ventilation rates greater than 80 L/min (Eves et al, 2005). The SCBA may also induce inspiratory and expiratory muscle fatigue, as demonstrated by reduced post exercise maximal mouth pressures (Eves et al, 2003b). Combined, these results suggest that the increased expiratory resistance may contribute to the ventilatory limitation during exercise due to an increase in the work of breathing or to a ventilatory constraint from an EFL as discussed in section 1.2. The presence of an EFL, increased work of breathing or increased exercising lung volumes has not been directly studied. Based on these findings, however, it is possible that the ventilatory limitation during exercise with the SCBA may be influenced by heliox breathing.

1.3.3 Effects of heliox breathing

Heliox breathing with the SCBA has only been reported in two papers. Eves and colleagues studied the effects of both normoxic and hyperoxic helium during submaximal (Eves et al, 2003b) and maximal (Eves et al, 2003a) exercise while wearing the SCBA. The normoxic helium gas (heliox) increased VO$_{2max}$ and maximal exercise ventilation as a result of a greater peak tidal volume compared to the compressed air mixture (Eves et al, 2003a). In both studies, the heliox gas mixture had the greatest effect on expiratory breathing resistance, expiratory flow rates, expiratory times, peak exercise ventilation, and respiratory muscle fatigue (Eves et al, 2003a; 2003b) which suggests that it has the greatest influence on ventilatory capacity. However, the effect of heliox on specific measures of ventilatory capacity with the SCBA has not been reported. Interestingly, the hyperoxic helium gas mixture had the greatest influence on VO_{2max} and peak power output (Eves et al, 2003a) and on submaximal ventilation rates (Eves et al, 2003b), indicating that this gas reduced the ventilatory limitation by the combined effect of improved ventilatory capacity and reduced ventilatory demand (through improvement in arterial oxygen content due to hyperoxic breathing; Eves et al, 2003a). As such, because the intent of the present thesis research was to modify ventilatory limitation through improving ventilatory capacity and not through reducing ventilatory demand, the normoxic helium gas (heliox) was chosen (as presented in Chapters 3 and 4). The major hypotheses arising from the review of literature related to the SCBA are presented in section 1.6.

1.4 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is "a respiratory disorder largely caused by smoking, which is characterized by progressive, partially reversible airway obstruction, systemic manifestations, and increasing frequency and severity of exacerbations" (O'Donnell et al, 2004). The characteristic symptoms of COPD are dyspnea and activity intolerance, which are accompanied by several systemic manifestations including skeletal muscle dysfunction and right heart failure (O'Donnell et al, 2004). The traditional belief was that the ventilatory limitations and symptoms of dyspnea during exercise precluded the ability of the muscles to perform work at a sufficient training intensity to obtain physiologic benefit (O'Donnell, 2001). In 1991, however, Casaburi and colleagues demonstrated that exercise training can elicit significant physiological benefits in patients (Casaburi et al, 1991). This was a landmark paper which has lead to the flood of new research examining non-traditional sources of exercise limitation in these patients. An understanding of each patient's source of exercise limitation is crucial in appropriate patient management (O'Donnell et al, 2004) and can have significant implications for exercise testing and training (Butcher and Jones, 2006; Gallagher, 1994).

The reasons for exercise limitation in patients with COPD have been reviewed extensively (Kealy et al, 2003; Aliverti and Macklem, 2001; Nici, 2000) and a summary of these limitations is presented in Appendix B (Butcher and Jones, 2006). In recent research, the major focus related to exercise limitation has been on either DH as a ventilatory limitation or peripheral muscle fatigue as a skeletal muscle limitation.

1.4.1 Dynamic hyperinflation

DH is a consequence of the EFL that patients with COPD exhibit (O'Donnell, 2006). Decreased in lung elastic recoil and reduced elastic tethering decrease airway diameter and increase airway resistance, causing the EFL (O'Donnell, 2006). Therefore, during low intensity activities or even at rest, EFL causes hyperinflation beyond resting FRC (Diaz et al, 2000). DH is associated with increasing sensations of dyspnea (O'Donnell et al, 2006; Marin et al, 2001) and an increased work of breathing during exercise (Yan et al, 1997a). The increased elastic work of breathing with DH is due to the decrease in dynamic lung and chest wall compliance at higher lung volumes (O'Donnell, 2006) as well as the effect of an inspiratory threshold load from intrinsic positive end expiratory pressure (Yan et al, 1997a). DH is an extremely important determinant of exercise intolerance in these patients. DH correlates quite closely with maximal (Diaz et al, 2000; O'Donnell et al, 2001) and submaximal (Marin et al, 2001) exercise tolerance in patients with COPD due to a reduction in the ability to expand tidal volume (O'Donnell et al, 2001). In a crucial study in this area, O'Donnell and colleagues (2001) studied the role of DH in exercise limitation of 105 patients with moderate to severe COPD (Forced expiratory volume in 1 second (FEV_1) 37% predicted). They found that 80% of patients demonstrated a significant degree of DH after incremental exercise and that the IC correlated closely with tidal volume ($r = 0.79$). The tidal volume response was primarily responsible for determining VO_{2max} ($r = 0.68$). Therefore, the constraints on tidal volume due to DH play an important role in exercise limitation in these patients.

O'Donnell and colleagues (2001) also found that patients often reach an EILV that very closely approximates but never quite reaches TLC (EILV approximately 94% of TLC) due to DH prior to exercise cessation. They termed the volume between this high EILV and TLC the 'minimal IRV' (IRV approximately 6% of TLC or 0.35 L) which indicates a constraint on tidal volume and an impending limitation on ventilatory capacity (O'Donnell et al, 2001). This minimal IRV could potentially be used as an indicator of the presence of a ventilatory limitation during exercise. The combination of increased work of breathing and ventilatory constraint with DH in patients may have significant implications for the development of skeletal muscle fatigue, as will be discussed below.

1.4.2 Skeletal muscle fatigue

Despite the traditional belief (and compelling evidence that demonstrates) that dynamic hyperinflation is the primary source of exercise limitation in patients with COPD, there is also a growing body of literature that implicates skeletal muscle fatigue as a primary cause of exercise limitation in some patients (presented below). Muscle fatigue is usually defined as any reversible loss in acute muscle force output and has both central and peripheral components (Gandevia, 2001). Peripheral fatigue is usually considered to be due to impaired muscle contractile function (Gandevia, 2001). Contractile muscle fatigue can be defined as "a reversible failure of working skeletal muscle to maintain a given force in response to neural stimulation" (Saey et al, 2006). Specific methods of fatigue measurement are not reviewed here, but are presented in Chapter 4 and in Appendix A. Quadriceps muscle fatigue is a common finding in some patients after cycle ergometry exercise, but not after walking (Man et al, 2003). As cycling is the most common mode of clinical exercise testing in COPD (ATS/ACCP, 2003), this section of the literature review will focus on changes occurring during and after cycling exercise.

There are several changes in skeletal muscles of patients with COPD that indicate muscle dysfunction and which can predispose these muscles to fatigue. These changes and the potential causes for them have been presented in recent reviews (Maltais et al, 2000; ATS/ERS, 1999). In brief, functional reductions in muscle strength (Bernard et al, 1998), endurance (Hul et al, 2004), and power (Yquel et al, 2006) are accompanied by several morphologic and metabolic changes that tend to reduce the oxidative capacity of the muscle (Maltais et al, 2000; 1996). Muscle endurance appears to be more affected than muscle strength (Hul et al, 2004), is significantly correlated with oxidative capacity (Allaire et al, 2004), and is associated with muscle fatigue, whereas muscle strength is not (Coronell et al, 2004).

Mador and colleagues (2000) found that approximately 50% of patients studied exhibited a significant level of quadriceps contractile fatigue after cycle ergometry exercise as assessed by twitch force measurement using magnetic femoral nerve stimulation. This finding has been confirmed subsequently (Mador et al, 2003; Saey et al, 2003; Saey et al, 2006). Although muscle fatigue is a normal consequence of cycling exercise in healthy subjects (So et al, 2005), the degree of muscle fatigue for a given oxygen consumption exhibited by patients is greater than that of age-matched healthy subjects (Mador et al, 2003) and is significantly associated with exercise tolerance ($r = 0.53$) (Saey et al, 2003). One potential mechanism that would cause the increase in muscle fatigue after cycling exercise in COPD patients is the increased WOB observed in these patients (Levison and Cherniak, 1968). As presented in section 1.2.2, increased respiratory muscle work during heavy exercise causes muscle fatigue in healthy subjects (Romer et al, 2006) that is likely due to a competition between the leg and respiratory muscles for blood flow (Dempsey, 2002). In some patients with COPD during incremental cycling exercise, leg blood flow plateaus despite increases in total body cardiac output, which suggests that blood flow was redistributed away from the working leg muscles (Simon et al, 2001). Because the WOB in patients with COPD can cause a respiratory muscle oxygen requirement of up to 40% of the total body oxygen consumption (Levison and Cherniak, 1968), it is likely that a considerable portion of the cardiac output is directed to the respiratory muscles. It has been suggested that the changes in oxygen delivery are due to changes in respiratory muscle work may be more important than the structural and functional changes that occur within the peripheral muscles of COPD patients in limiting exercise tolerance (Richardson et al, 1999). The plateau in leg blood flow and the limitation on oxygen delivery resulting from ventilatory limitation, however, may be a cause of leg muscle fatigue after cycling exercise in patients with COPD; but, this has not been reported. Overall, these findings indicate that skeletal muscle fatigue is an important consequence of exercise in some COPD patients.

What is most interesting is the fact that not all patients demonstrate muscle fatigue. It has been suggested that the oxidative profile of those who fatigued was worse than those who did not (Saey et al, 2005), which suggests another potential mechanism causing fatigue. An alternative explanation for the disparity in fatigue response between patients could be related to the primary mechanism for exercise limitation. Saey and colleagues (2003) studied the response to bronchodilator administration on exercise tolerance and quadriceps contractile fatigue in 18 patients with moderate to severe COPD (FEV_1 38% predicted). They found that the inhalation of a bronchodilator increased exercise tolerance and level of muscle fatigue only in those subjects who did not fatigue their leg muscles after inhalation of a placebo. Because the bronchodilator improved lung function (FEV_1) in both groups of subjects, it was suggested that the group who did not fatigue were likely more limited by constraints on ventilatory capacity than on muscle fatique (Saey et al, 2003). Therefore, ventilatory factors likely limited exercise tolerance prior to the development of leg muscle fatigue in this group. The degree of ventilatory constraint, however, was not measured in this study and therefore, the relationship between the degree of ventilatory limitation and skeletal muscle fatigue is not known. Also, although the mean increase in FEV_1 with the bronchodilator was approximately 12 ± 18% (Saey et al, 2003), it is possible that the marginal clinical significance of the change in FEV_1 (Pellegrino et al, 2005) and the high degree of variability indicates that some subjects did not improve lung function enough to impact the degree of ventilatory constraint during exercise. Therefore, the use of a bronchodilator to improve ventilatory constraint may not have been adequate in all patients, making classification of individual subjects' exercise limitations difficult. The ability to classify subjects into those who are ventilatory limited or those who are leg muscle limited would have significance in clinical exercise testing and for exercise rehabilitation. Perhaps the use of another method of relieving the ventilatory constraint, such as heliox (Palange et al, 2004), would show more consistent results on ventilatory function and help clarify the importance of the balance between ventilatory constraint and skeletal muscle fatigue in these patients and this is the subject of Chapter 4.

1.4.3 Effects of heliox breathing during exercise

In patients with COPD, normoxic heliox breathing has been shown to have either no effect on exercise tolerance (Johnson et al, 2002), an increase in VO_{2max} (Richardson et al, 1999; Oelberg et al, 1998), or an increase in time to exhaustion during moderate intensity (60% of peak work rate) (Eves et al, 2006) and high intensity (80% of peak work rate) (Palange et al, 2004) constant work rate cycling. The only obvious difference between studies that might explain why Johnson and colleagues did not demonstrate differences in exercise tolerance whereas the other four studies did is that Johnson et al used a treadmill incremental protocol, whereas the other three used cycling. There are distinct differences observed in the ventilatory response to exercise between walking and cycling (Palange et al, 2000), which might explain the discrepancy. Disease severity does not seem to play a role as subjects in the Johnson et al (2002) study had severe COPD (FEV_1 34% predicted) whereas the subjects in the Oelberg et al (1998) study had very severe COPD (FEV_1 19% predicted) and the subjects in the other three studies had less severe disease (Eves et al, 2006; Palange et al, 2004; Richardson et al, 1999).

It is evident, however, from the wide variability of response to exercise tolerance observed in all of the above studies, that part of the reason is the fact that not all subjects seem to respond to breathing heliox. Saey et al (2003) suggested that the response to modifying ventilatory limitation with a bronchodilator is modulated by the presence of contractile fatigue. It is possible that similar findings would explain the variability in the response to heliox; however, this has not been reported.

To my knowledge, the only studies demonstrating an effect of normoxic heliox on lung mechanics and ventilatory constraint during exercise in patients with COPD were Eves et al (2006) and Palange et al (2004). Associated with the increase in constant work rate exercise time with heliox was a 12% (Eves et al, 2006) and a 11% (Palange et al, 2004) increase in IC (r = 0.89

and r = 0.70, respectively) at isotime (the time that each subject stopped exercise on the room air test). Palange et al (2004) studied 12 patients with moderate to severe COPD (FEV_1 38% predicted). In addition to the increase in IC at isotime was a 48% increase in IRV, which indicates relief of the ventilatory constraint from both below and above. This relief allowed a 7% greater tidal volume response at peak exercise on heliox, but no change at isotime (Palange et al, 2004). In contrast, Eves et al (2006) found no change in IRV at isotime or peak exercise, despite the increased IC, the effect of which being a 12% increase in tidal volume at isotime. Eves and colleagues (2006) studied less severe COPD (FEV_1 47% predicted), which may explain some of the difference in response. At symptom limited peak exercise in both studies, IRV reached a level with heliox similar to that on the room air test, indicating that the peak level of ventilatory constraint was similar between the two gas mixtures. Eves et al (2006) also studied the effects of both normoxic heliox and hyperoxic helium (40% O_2, 60% He) on the work of breathing in patients with COPD. They found that only the hyperoxic helium gas mixture reduced the total work of breathing at isotime, presumably through a reduction in ventilatory requirement (hyperoxia) and an increase in ventilatory capacity (helium) (Eves et al, 2006). In contrast, the normoxic heliox gas did not significantly alter total work of breathing at isotime despite improvements in IC and reductions in peak inspiratory esophageal pressures (Eves et al, 2006). In this case, heliox was more effective in reducing ventilatory constraint than in affecting work of breathing. However, heliox has been shown to be effective in reducing total work of breathing in patients at rest (Eves et al, 2006; Gainnier et al, 2003). Overall, the findings from the above studies suggest that heliox is an effective method of delaying ventilatory limitation during cycling exercise, but will not remove it completely.

The effect of delaying ventilatory limitation during exercise with heliox on muscle fatigue in patients with COPD has not been reported. There are two possible responses that may be observed depending on the mechanism of action of heliox on ventilatory capacity. The first, based on the findings of Saey et al (2003), would be that delaying the ventilatory constraint would allow an increased exercise tolerance and a subsequent increase in peripheral muscle fatigue at symptom limitation. The second, based on the findings of Romer et al (2006) in healthy subjects, would be that if the work of breathing were reduced with heliox , the level of peripheral muscle fatigue would be decreased at isotime, presumably through an increase in leg muscle blood flow. Although the intent of this thesis research was not to determine the cause of muscle fatigue or to measure the effects of heliox on work of breathing in patients with COPD, the observations may provide some indirect evidence on the mechanisms. This research will, however, examine the relationship between the presence of ventilatory limitations and skeletal muscle fatigue in patients with COPD. The major research questions arising from the review of literature related to COPD are presented in section 1.6

1.5 SUMMARY

Reductions in ventilatory capacity that occur in subjects wearing the self-contained breathing apparatus and in patients with COPD have a significant effect during exercise. Increased expiratory resistance and the presence of expiratory flow limitation have been shown to increase exercising lung volumes through reductions in inspiratory capacity. Increased lung volumes during exercise significantly increase work of breathing and can potentially impose a ventilatory constraint on the expansion of tidal volume. Although this effect has been demonstrated in patients with COPD, it is unknown to what degree these reductions in ventilatory capacity occur in subjects wearing an SCBA. Breathing heliox has been shown to increase exercise tolerance in subjects wearing an SCBA and in patients with COPD. In patients with COPD, this increase in exercise tolerance is associated with significant changes in ventilatory capacity; however, the effect of this on ventilatory capacity has yet to be determined in subjects wearing an SCBA. Finally, in contrast to the traditional view that patients with COPD are primarily limited by their ability to increase ventilation during exercise, some patients exhibit peripheral muscle fatigue as a primary limiting factor during exercise. It is unknown, however, to what extent limitations due to ventilatory contraints are related to those due to muscle fatigue. Delaying ventilatory limitation should have a significant effect on leg muscle fatigue and provide some insight into the integrative mechanisms of exercise limitation in this population.

1.6 STATEMENT OF PURPOSE

The underlying aim of the three research studies conducted for this thesis was to examine selected aspects of the nature and the impact of limitations on ventilatory capacity during exercise. Subjects wearing an SCBA and patients with COPD were chosen as two populations who are known to demonstrate reduced expiratory flow and ventilatory limitation during exercise and also because the results of these studies could provide practical information regarding either occupational performance or exercise rehabilitation.

1.6.1 STUDY ONE: Work of breathing is increased during exercise with the self-contained breathing apparatus regulator

Although reductions in peak ventilation during exercise occur while wearing an SCBA, the nature of this ventilatory limitation is unknown. Prior to studying the effects of modifying the ventilatory limitations, it is important to document the mechanisms behind the changes in ventilatory capacity. The aim of this study was to examine the components of work of breathing and to detail the respiratory mechanics of subjects breathing from an SCBA regulator during cycling exercise. As such, this study was designed to test the following hypotheses:

(1) WOB will increase with the SCBA regulator;
(2) Resistive work performed by the expiratory muscles will be a major contributor to total WOB
(3) The increase in WOB will be accompanied by changes in ventilatory constraint.

1.6.2 STUDY TWO: Impairment of exercise ventilatory mechanics with the self-contained breathing apparatus (SCBA) is improved with heliox breathing

If a significant alteration in ventilatory mechanics occurs with the SCBA during cycling exercise, these effects should also be present during exercise that is more specific to firefighting, such as stair stepping. These effects on ventilatory mechanics may be due to changes in maximal expiratory flow rate, and may cause respiratory muscle fatigue. Heliox breathing has been shown to increase maximal exercise ventilation and improve exercise performance, suggesting that exercise is ventilatory limited. If this limitation is due to reduced ventilatory capacity, heliox should have a significant effect on the above variables. The aim of this study was to examine the effects of the SCBA on ventilatory mechanics, WOB, respiratory muscle fatigue, and pulmonary function; and to examine the effects of breathing heliox on the same variables. Study two was designed to test the following hypotheses:

(1) The SCBA regulator will increase exercise WOB and respiratory muscle fatigue, and impair pulmonary function and ventilatory mechanics;
(2) Replacing compressed air with heliox in the SCBA will, at least partially, reverse these effects.

1.6.3 STUDY THREE: Interaction between ventilatory constraint and contractile muscle fatigue during cycling exercise in patients with COPD

There are two primary schools of thought related to exercise limitation in patients with COPD. The first maintains that these patients are usually limited by their ability to increase ventilation during exercise. The second has shown that some patients may be limited by the presence of leg muscle fatigue. The aim of this final thesis study was to examine the relationship between measures of ventilatory limitation and leg muscle fatigue. Study three was designed to test the following hypotheses:

(1) Delaying ventilatory constraint with heliox will increase exercise tolerance and leg muscle fatigue;

(2) The delay in ventilatory constraint will cause a greater increase in exercise tolerance and leg muscle fatigue in those patients who are not limited by leg muscle fatigue during room air breathing.

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CHAPTER TWO

VENTILATORY MECHANICS WITH THE SELF-CONTAINED BREATHING APPARATUS

2.1 INTRODUCTION

The self-contained breathing apparatus (SCBA), worn by firefighters and other workers for respiratory protection, has been shown to reduce maximal ventilation during heavy work, an effect that is primarily due to the external expiratory resistance of the regulator (Eves et al, 2005). Eves et al. (2003a) showed that at ventilation rates above 80 $L \cdot min^{-1}$, greater expiratory pressure was required in order to maintain ventilation. As well, maximal tidal volume occurred at a ventilation rate of 110 $L \cdot min^{-1}$, and further increases in ventilation were achieved by increasing respiratory rate. They also showed that breathing helium-based gas mixtures increased exercise performance and maximal ventilation rate. Together, these findings confirm that the SCBA imposes a limitation on ventilation during heavy to maximal exercise. Sothmann et al (1992) speculated that the SCBA would increase the work of breathing during heavy exercise. Eves et al (2005) lend support to this suggestion by finding a greater expiratory resistance with the SCBA, which hinders the ability to achieve high ventilation rates during heavy work. Work of breathing can be separated into resistive and elastic components during both inspiration and expiration. It could be expected, then, that the expiratory resistance of the SCBA would cause an increase in the expiratory resistive work. To my knowledge, however, neither the work of breathing nor a detailed description of respiratory mechanics during exercise with the SCBA has been reported.

The work of breathing (WOB) can be calculated by the use of Campbell diagrams to plot the changes in esophageal pressure and lung volume over a single breath (Roussos and Campbell, 1986). Measurement of expired volume with the SCBA has been previously reported (Eves et al, 2002), however; since the inspired volume is delivered from a compressed air tank to the regulator through a high pressure line, measurement of inspiratory volume is technologically challenging. In order to overcome this problem, we used whole body, constant volume plethysmography to measure inspired and expired lung volume throughout the respiratory cycle using a method similar to that of Stubbing et al (1980). The aim of this study was to examine the components of work of breathing and to detail the respiratory mechanics of subjects breathing from an SCBA regulator during exercise. I hypothesized that the WOB would increase with the

SCBA regulator when ventilation exceeded 80 $L \cdot min^{-1}$ and that the resistive work performed by the expiratory muscles (active expiratory resistive WOB) would make a significant contribution to total WOB at these higher ventilation rates.

2.2 METHODS

Subjects

Twelve healthy male subjects volunteered to participate in this study, which was previously approved by the University of Alberta Health Research Ethics Board. Subject characteristics are presented in Table 2-1. All subjects were experienced in the use of the SCBA and were able to achieve a peak work rate of at least 275 Watts on a graded exercise test. Prior to involvement in this study, each subject provided written informed consent.

Spirometry and graded exercise test

Baseline spirometry, using a standard rubber mouthpiece, and a graded exercise test were completed at the first visit. Spirometry (forced vital capacity and forced expiratory volume in one second) was performed to American Thoracic Society (1995) standards using a dry-rolling spirometer (Sensormedics, Yorba Linda, CA) and the best of at least three forced vital capacity trials was used in the analysis.

The graded exercise test was performed on an electronically braked cycle ergometer (Sensormedics Ergometrics 800S, Yorba Linda, CA) while the subject wore an SCBA facepiece (AV-2000 assembly, Scott Health and Safety, Monroe, NC) to which a low resistance breathing valve (RV) was attached (2700 Series, Hans Rudolph, Kansas City, MO). The expired gas was ducted into a calibrated metabolic cart (TrueOne, Parvomedics, Salt Lake City, UT) and metabolic measurements were averaged every minute. Heart rate was recorded using telemetry (Polar USA Inc., CT). The test began at 100 Watts and increased by 25 Watts/minute until voluntary exhaustion. The highest minute VO_2 obtained on this test was accepted as maximal oxygen consumption (VO_{2max}).

Experimental protocol

During a second visit, two randomized exercise trials, separated by at least one hour of rest were completed. In one trial, the subject used a low resistance breathing valve attached to the SCBA facepiece (RV condition), and in the other, the SCBA regulator assembly (BA condition). Subjects were not blinded to the condition they were using as it would be obvious when a subject is breathing from the SCBA. In the BA condition, subjects breathed compressed air through a Scott E-Z FLO positive pressure regulator. The regulator was connected to a Scott pressure-reducing regulator which was attached to a Scott 4.5 Air-Pak cylinder. Since we were interested in studying the effects of the SCBA regulator alone, without any additional effects from the harness and back frame, the tank was secured to the floor of the body box. Each exercise trial consisted of five minutes of rest followed by four minutes of continuous exercise at both 150 and 180 Watts, and three minutes at both 210 and 240 Watts.

Modifications to the SCBA assembly

Two modifications were made to the SCBA facepiece and regulator to facilitate physiologic measurements. These modifications did not affect the normal operation of the SCBA regulator as verified by a qualified Scott technician. First, a plexiglass cone was sealed over the regulator as previously described (Eves et al, 2002 and shown in Figure 2-1) to attach a gas collection hose. Second, the voice ports on the facepiece were replaced by heavy gauge metal discs to collect mask and esophageal pressure data. The disc for measuring mask pressure had a nipple to which transducer tubing was connected as previously described (Eves et al, 2002). The disc for measuring esophageal pressure had a port wide enough to allow passage of an esophageal balloon catheter. A rubber stopper with a longitudinal slit and a hole for the catheter was inserted into the port to prevent air leakage.

Inspiratory and expiratory tidal volumes

To directly determine inspiratory tidal volume without modifying the SCBA assembly, a body plethysmograph (body box) was built to accommodate a cycle ergometer. More detailed methodology related to the construction of this body box is presented in Appendix A. The box (2.13 m high, 1.22 m long, 0.76 m wide and an internal volume of approximately 2700 L) was constructed of 19 mm plywood and 13 mm plexiglass. Electromagnets were used to seal the door and permit rapid access to the subject, if needed. Several airtight ports in the box wall allowed the connection of gas collection and pressure measurement tubing.

Pressure inside the box was measured by a differential pressure transducer (MP45 ±50 cmH_2O, Validyne, Northridge, CA) connected using 5 mm ID tubing. The pressure transducer was connected to an amplifier (Model MC 1-3, Validyne, Northridge, CA) and data were collected at 200 Hz using an automated digital chart recorder (Powerlab 8SP and Chart version 4.2, ADI Instruments Inc, Colorado Springs, CO). To account for thermal drift of box pressure, a small plexiglass compensation chamber was placed inside the body box and connected to the negative port on the box pressure transducer. The compensation box was sealed except for a small port the size of a 25 gauge needle. Thus, slow thermal increases in box pressure were subtracted from the faster positive and negative pressure measurements that occurred secondary to changes in chest wall dimensions during breathing.

For the BA condition, the compressed air tank provided the inspired air. For the RV condition, inspired air was ducted from the exterior of the box using 3.8 cm corrugated tubing. For both conditions, the exhaled gas was ducted to the exterior of the box. Box volume changes were calibrated by having the subject hold his breath at end tidal expiration while air was pumped into and out of the box with a 3-L syringe at varying flow rates. Box pressure changes were measured and then calibrated for volume. Respiratory rate, tidal volumes, ventilation rates, peak and mean flow rates, and duty cycle (inspiratory time/total time [T_I/T_{TOT}]) were measured during the last minute of each workload.

Physiological measurements

All pressure data were measured using differential pressure transducers (MP45 ±50 cmH_2O, Validyne, Northridge, CA). The frequency response for the pressure transducers and their associated tubing and connectors was linear up to 5 Hz. Esophageal pressure (Pes) was measured through a 10cm esophageal balloon (Ackrad Laboratories Inc., Cranford, NJ) according to standard procedure (Milic-Emili et al. 1964). The proximal end of the esophageal catheter was passed through the port in the SCBA facepiece and sealed as described above. Esophageal pressure data were collected continuously throughout the protocol. Mask pressure (Pm) was measured through tubing connected to the mask pressure disc in the voice port. External breathing resistance was estimated by dividing the mean expiratory mask pressure by the mean expiratory flow rate from the body box measurements. For esophageal and mask pressure responses, peak pressures and pressure swings were used in the analysis. Pressure swings were calculated from the difference between peak expiratory and peak inspiratory pressures.

Inspiratory capacity and lung volumes

Changes in end-expiratory lung volume (EELV) were estimated from measurements of inspiratory capacity (IC) taken at rest and during the last minute of each workload. This technique assumes that vital capacity does not change during exercise (Stubbing et al. 1980) or while wearing the SCBA regulator. The latter assumption was confirmed during pilot work.

Confirmation of adequate IC efforts was achieved by ensuring that peak inspiratory esophageal pressures were consistent across IC maneuvers. EELV was calculated by subtracting IC from vital capacity obtained at rest. End inspiratory lung volume (EILV) was estimated by adding tidal volume to the EELV. Changes in EELV and EILV were expressed as a percentage of vital capacity. This technique does not measure the actual EELV and EILV as total lung capacity is unknown, but estimates them from a known vital capacity.

Work of breathing

The active muscular WOB was estimated by using modified Campbell diagrams (Roussos and Campbell, 1986) as illustrated in Figure 2-2. From the esophageal pressure and tidal volume data at the zero flow points of each level of ventilation (including the largest tidal volumes) during rest and exercise, a lung compliance curve was created for each subject (line through points BE). The average esophageal pressure-volume relationship at end expiratory lung volume at rest while in the RV condition was used to determine the pressure volume response at functional residual capacity (FRC, point A). Similar to the procedures used by Sliwinski et al, (1998) and Yan et al, (1997), chest wall compliance was estimated for each subject using published data based upon age (Estenne et al, 1985) and was then extrapolated through the pressure-volume point at FRC to the volume at EILV and EELV (line through points DC). For each level of ventilation, pressure-volume loops were placed upon the compliance curves. A line was drawn from the end inspiratory lung volume (point B) on the lung compliance curve to the point at the corresponding lung volume on the chest wall compliance curve (point C). A second line was drawn (if changes in EELV from FRC were observed) from the EELV (point E) on the lung compliance curve to the corresponding point on the chest wall compliance curve (point D). As such, the pressure-volume loop can be partitioned into four distinct areas representing different types of work. The area ABCA represents the work required by the respiratory muscles to overcome the elasticity of the lung (inspiratory elastic work). The area AFBA represents the muscular work required to overcome airflow resistance during inspiration (inspiratory resistive work). The area ADEA represents the work required by the expiratory muscles to overcome the elastic outward recoil of the chest wall to achieve an end expiratory lung volume below functional residual capacity (expiratory elastic work). The area AGEA represents the work required to overcome airflow resistance (intrathoracic and extrathoracic) during expiration (active expiratory resistive work) (Roussos and Campbell, 1986).

Pressure-volume loops were generated as close to the end of each stage of exercise as possible. The average of three breaths was used in the analysis. These breaths were selected as those that most closely matched the mean values for tidal volume and peak esophageal pressures for that level of work and were averaged. Each area was measured manually using a polar planimeter (Keuffel and Esser, Germany) until each measurement was reproducible within 0.75 $cmH_2O \cdot L$. The researcher responsible for analyzing these tracings was blinded to the condition under which each pressure-volume loop was collected. Values were expressed as the work rate per minute (work per loop multiplied by the average respiratory rate in the last minute of each stage). Each of the four components of WOB was analyzed separately. Total WOB (the sum of the four components) was also calculated and included in the analysis.

Statistical Analysis

A 2 (condition) x 4 (work load) repeated measures ANOVA was used to determine the effects of the SCBA regulator on the WOB compared to the low resistance breathing valve. When a significant effect was detected, a Tukey's post hoc multiple comparisons test was used to compare conditions directly. A Pearson's product-moment correlation analysis was used to examine the relationship between work of breathing and pressure data. An alpha value of <0.05 was considered significant for all analysis and post hoc tests. Data are presented as mean (±SD) unless specified. All analyses were completed using Statistica version 6.1 (StatSoft Inc, Tulsa, OK).

Sample size calculation

Eves et al (2005) previously found that breathing resistance (a crude indicator of WOB) was greater with the SCBA regulator compared to a low resistance valve (4.0 ± 0.6 vs. 2.7 ± 0.4 $cmH_2O \cdot s \cdot L^{-1}$, respectively). Using these values, an alpha of 0.05 and a power of 0.80, it was estimated that 3 subjects are needed to demonstrate significant differences.

2.3 RESULTS

Work of breathing

Figure 2-3 shows the results of the analysis of WOB. No significant differences between the BA and RV were observed for any components of the WOB at 150W. Inspiratory resistive work (Figure 2-3A) was unaffected by the SCBA at any exercise intensity. Significant differences were found in active expiratory resistive work (Figure 2-3B at 240 Watts; 881 ± 359 vs. 572 ± 229 $cmH_2O \cdot L \cdot min^{-1}$). This indicates a 59% increase in active expiratory resistive work (range 7 – 161%) with the SCBA regulator. Inspiratory elastic work (Figure 2-3C) was significantly increased with the SCBA at 180, 210, and 240 W (32% at 240 W, range -9 – 94%). There were also significant decreases in expiratory elastic work (Figure 2-3D) against the chest wall at 180 and 210 W ($p<0.05$). At 240 W ($V_E = 112 \pm 17$ L·min^{-1} in the BA condition), the increased active expiratory resistive work and inspiratory elastic work contributed to a 13% (range -14 – 51%) increase in total WOB (3248 ± 1034 vs. 2881 ± 878 cmH$_2$O·L·min^{-1}; $p<0.05$) in the BA condition (Figure 2-3E). Correlational analysis revealed that the degree of individual differences in work of breathing was not correlated with age, pulmonary function, fitness level, breathing patterns, breathing resistance, or flow rates.

Mask pressure swing and peak expiratory mask pressures were significantly greater in the BA condition ($p<0.05$, Figure 2-4). Mask pressure swing was highly correlated with total WOB ($r = 0.81$, $p<0.05$). Esophageal pressure swing and peak expiratory pressure were significantly greater in the BA condition ($p<0.05$). Esophageal pressure swing was highly correlated with total WOB (total WOB = 124·esophageal pressure swing – 1553 cmH$_2$O·L·min^{-1}; $r = 0.91$, $p<0.05$).

Lung volumes, ventilation, and heart rate

Tidal volume, respiratory rate, ventilation, and heart rate were not different between the two conditions at any work load (Table 2-2). Figure 2-5 shows the mean lung volumes at comparable ventilation rates throughout the exercise protocol. Compared to resting values, end-inspiratory lung volume increased and end-expiratory lung volume decreased in each work load. However, these lung volumes were higher while wearing the SCBA regulator than with the low resistance valve at 180 W and higher. In the BA condition, end-inspiratory lung volume plateaued at approximately 90% of the mean vital capacity at a ventilation rate of 73.7 ± 11.0 L·min^{-1} and there were no further increases in tidal volume despite increases in ventilation. In the RV condition, tidal volume increased ($p<0.05$) progressively throughout exercise reaching end inspiratory lung volume of 85% vital capacity at the final work load.

Flow rates, breathing resistance, and duty cycle

Peak inspiratory and expiratory flow rates were not significantly different between conditions; however, mean expiratory flow rate was significantly lower at 240 Watts in the BA condition. Figure 2-6 shows a decrease in mean expiratory flow (3.17 ± 0.96 vs. 3.69 ± 0.41 L·s^{-1} vs. the RV condition) at 112 L·min^{-1} of ventilation in the BA condition. Expiratory breathing resistance (Figure 2-6) was significantly greater and duty cycle (Table 2-2) was significantly lower in the BA condition across all work loads.

2.4 DISCUSSION

The effects of the SCBA regulator on WOB during exercise

The results of this study support the hypothesis that, at high ventilation rates, WOB is increased with the SCBA regulator compared to a low resistance breathing valve. At a mean ventilation of 55.0 ± 8.9 $L \cdot min^{-1}$ in the BA condition, inspiratory elastic work was increased, and remained greater than the RV condition for the remainder of the protocol. During the final work load, a ventilation rate of 112.0 ± 16.6 $L \cdot min^{-1}$ in the BA condition elicited, on average, a 26.3 ± 24.2% increase in inspiratory elastic work, a 58.7 ± 51.1% increase in active expiratory resistive work, and a 12.7 ± 11.6% increase in total WOB. These are new findings, since, to my knowledge, measurement of WOB with the SCBA regulator has not been previously reported.

One of the more unexpected findings of this study was the increase in inspiratory elastic work with the SCBA regulator (Figure 2-3). Although tidal volume was not significantly greater with the SCBA (Table 2), the increased end-expiratory lung volume resulted in a higher end-inspiratory volume and an increased inspiratory elastic work. End-inspiratory lung volume approached 90% of total lung capacity at a ventilation rate of 73.7 $L \cdot min^{-1}$ and then stayed at that level for the remainder of the protocol (Figure 2-5). Therefore, as subjects approached total lung capacity, they were breathing more on the flat portion of the lung compliance curve, which at least partially explains the increased inspiratory elastic work (Martin et al, 1980).

The mechanisms behind the increased lung volumes are unknown. Normally, tidal volume increases during exercise through a combination of an increase in EILV and a decrease in EELV. The decrease in EELV prevents a disproportionate rise in inspiratory elastic work, which would occur if tidal volume increased only through an increase in EILV, and optimizes the length-tension relationship of the inspiratory muscles (Roussos and Campbell, 1986). This compensatory mechanism, however, increases the amount expiratory muscle work performed in order to overcome the elastic recoil of the chest wall (expiratory elastic work). In the presence of increased expiratory resistive work, the total amount of expiratory muscle work would be increased even further, perhaps to intolerable levels. It is possible that the higher lung volumes while wearing the SCBA regulator occur in order to minimize the total amount of expiratory muscle work by decreasing the expiratory elastic work (Figure 2-3D). This speculation is in line with the findings of McClaran et al, (2002) who examined the effect of an external expiratory flow limitation (through the use of dead space tubing) on lung volumes, ventilation and exercise limitation. They demonstrated that exercising lung volumes increased prior to the development of the expiratory flow limitation indicating that the resistance created by the tubing, and not merely the flow limitation, was an important contributor to the change in lung volumes.

Eves et al (2003b) suggested that dynamic hyperinflation may occur while wearing the SCBA and may be a limiting factor to increasing tidal volume during exercise. Although the present study demonstrated that a plateau in tidal volume occurs and that exercise lung volumes were greater with the SCBA, dynamic hyperinflation did not occur except in one subject who also hyperinflated with the low resistance valve. The increase in lung volumes, however, may still be a limiting factor as EILV reached approximately 90% of vital capacity and EELV appeared to plateau at a higher lung volume than the RV condition. If this subtle difference in pattern of exercise lung volumes with the SCBA continues up to maximal exercise, there may be an earlier mechanical constraint on tidal volume expansion (O'Donnell et al, 2001) and may contribute to the limitation on ventilation observed with the SCBA (Eves et al, 2005).

An increase in the active expiratory resistive work was expected as the SCBA regulator imposes an increase in breathing resistance on expiration (Eves et al, 2005) (Figure 2-6). However, active expiratory resistive work increased in a similar fashion in both the BA and RV conditions up to and including a ventilation of 88 $L \cdot min^{-1}$, despite significantly greater mask pressures and breathing resistance at lower ventilations in the BA condition. As lung volumes were higher in the BA condition, it is possible that the decreased airway resistance and increased lung elastic recoil that occur with increased lung volume (Roussos and Campbell, 1986) were sufficient to offset the effect of the external breathing resistance at lower work loads. There were no differences in active inspiratory resistive work between the two conditions suggesting that the positive pressure delivery system of the SCBA regulator does not unload the inspiratory muscles. As well, because duty cycles were lower in the BA condition, the work on inspiration was performed over a shorter time than in the RV condition, suggesting that the inspiratory power required during exercise with the SCBA regulator was greater than that with the low resistance breathing valve.

The significance of increased work of breathing on exercise performance

An increase in work of breathing can decrease exercise performance due to increases in the sensation of breathlessness and/or lung hyperinflation (Iandelli et al, 2002) or to a competition between respiratory muscles and exercising leg muscles for blood flow at maximal exercise. Iandelli et al (2002) compared the effect of imposing a mechanical flow limitation with unencumbered breathing during exercise on ventilatory mechanics and blood volume shifts from the thorax. Under the flow limitation condition, exercise was limited primarily by sensations of dyspnea, which were caused primarily by the large expiratory muscle pressures exerted during exercise. Although expiratory resistive work was not measured in that study, it is likely safe to assume that it was increased. It was suggested that the large increases in intrathoracic pressure reduced venous return and likely impaired stroke volume (Iandelli et al, 2002). In line with this possibility, Stark-Leyva et al, (2004) found that during exercise with expiratory loading, stroke volumes, and ultimately cardiac output, were decreased primarily by increases in intrathoracic pressure. The degree of expiratory loading with the SCBA, although significant, is less than half of that observed by Stark-Leyva et al, (2004). A difference between loaded and unloaded breathing of 10 cmH_2O measured at the mouth was applied by Stark-Leyva, whereas the difference between the two conditions in the present study was between 3 and 4 cmH_2O. Therefore, it is possible that the use of the SCBA regulator during exercise reduces cardiac output, however; this possibility requires further study.

Another potential consequence of an increased work of breathing is the competition for available cardiac output. Harms et al, (1997;1998;2000) examined the effects of increasing inspiratory work of breathing on exercise performance, cardiac output, and the distribution of cardiac output during maximal and submaximal exercise. In summary, at maximal exercise, the increase in respiratory muscle work led to a competition for blood flow between the exercising leg muscles and the respiratory muscles. They suggested that this competition leads to a reduction in leg muscle blood flow and leg muscle oxygen consumption, which would ultimately result in muscle fatigue (Harms et al, 1997). Romer et al, (2006) who demonstrated that greater inspiratory muscle work leads to greater levels of peripheral muscle fatigue after high intensity exercise have subsequently confirmed this suggestion. We speculate that alterations in inspiratory elastic and expiratory resistive work as demonstrated with the SCBA regulator would result in a similar effect on leg blood flow and leg muscle fatigue, however, further study is required to assess this possibility.

2.5 CONCLUSIONS

We studied the effect of the SCBA regulator on the WOB during exercise and found that total WOB was increased at ventilation rates above 112 $L \cdot min^{-1}$, due to the relative contributions of increased inspiratory elastic and active expiratory resistive work. There were no changes in active inspiratory resistive or expiratory elastic work at this ventilation rate. The increases in lung volume during exercise with the SCBA regulator increase inspiratory elastic work and may contribute to a limitation in ventilation during very heavy exercise but there is little effect on the total WOB at light and moderate exercise intensities.

ENDNOTE:

A version of this chapter has been published. Butcher SJ, Jones RL, Eves ND, Petersen SR. Work of breathing is increased during exercise with the self-contained breathing apparatus regulator. Appl Physiol Nutr Metabolism. 31:693-701, 2006.

Table 2-1: Subject characteristics

Characteristic	Mean	SD	Range
Age (years)	32.3	9.8	22 - 53
Height (cm)	181.1	5.9	168 - 189
Weight (kg)	87.4	10.8	70 - 104
VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$)	43.1	4.1	36.9 - 53.0
POpeak (W)	314.6	29.1	275 - 350
$V_E$peak ($L \cdot min^{-1}$)	154.3	27.3	115.6 - 204.6
$V_T$peak (L)	3.68	0.42	2.62 - 4.16
FVC (L)	5.8	0.6	4.9 - 6.7
FVC (% predicted)	103.8	8.3	88.7 - 115.9
FEV_1 (L)	4.8	0.5	3.7 - 5.4
FEV_1 (% predicted)	111.8	12.5	85.6 - 126.7
FEV_1/FVC	0.80	0.10	0.76 - 0.92

POpeak = peak power output on the graded exercise test, $V_E$peak = peak ventilation rate on the graded exercise test, $V_T$peak = tidal volume peak on the graded exercise test, FVC = forced vital capacity, FEV_1 = forced expiratory volume in one second.

Table 2-2. Results of the analysis comparing the SCBA (BA condition) and the low resistance breathing valve (RV condition) for physiologic measurements during exercise.

	150W		180W		210W		240W	
	BA	RV	BA	RV	BA	RV	BA	RV
V_E	55.0	58.5	73.7	76.9	88.2	93.1	112.0	119.1
($L \cdot min^{-1}$)	(8.9)	(6.8)	(11.0)	(9.9)	(12.8)	(13.0)	(16.6)	(12.0)
V_T	2.67	2.61	2.88	2.84	3.07	2.91	3.08	3.03
(L)	(0.35)	(0.35)	(0.33)	(0.33)	(0.38)	(0.34)	(0.43)	(0.38)
RR	21	23	25	27	30	32	37	38
(breaths/ min)	(5.0)	(4.4)	(6.0)	(5.2)	(7.3)	(6.9)	(8.2)	(7.6)
HR	137	137	153	155	167	169	180	180
(bpm)	(18.2)	(15.3)	(15.8)	(15.4)	(14.6)	(14.5)	(12.9)	(12.7)
T_I/T_{TOT}	0.41*	0.46	0.40*	0.45	0.39*	0.46	0.39*	0.46
	(0.05)	(0.03)	(0.06)	(0.03)	(0.04)	(0.03)	(0.04)	(0.03)

Values are mean (SD). BA = SCBA, RV = low resistance breathing valve, V_E = minute ventilation, V_T = tidal volume, RR = respiratory rate, HR = heart rate, T_I/T_{TOT} = duty cycle, bpm = beats per minute. *significant difference from the RV condition for the corresponding work rate, $p<0.05$.

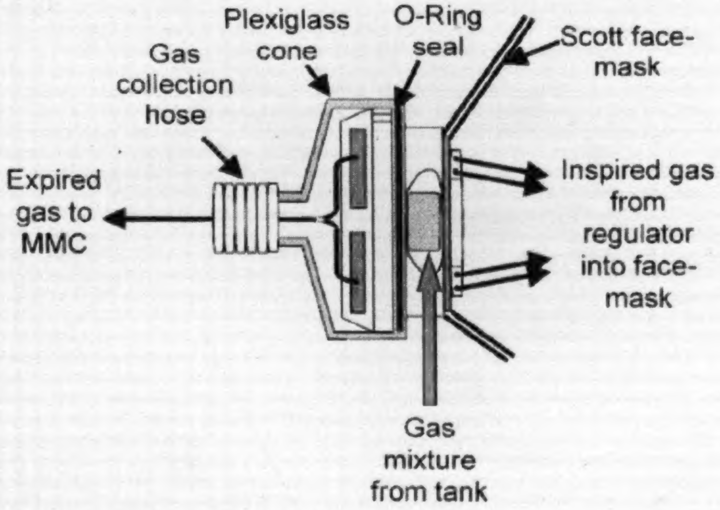
Plexiglass cone
O-Ring seal
Scott face-mask
Gas collection hose
Expired gas to MMC
Inspired gas from regulator into face-mask
Gas mixture from tank

Figure 2-1. Schematic of the SCBA regulator. Shown are the components of the regulator, the attachment of a Plexiglas cone, and the attachment of gas collection tubing to lead to a metabolic measurement system or to the exterior of the body box. Reproduced from Eves et al (2002).

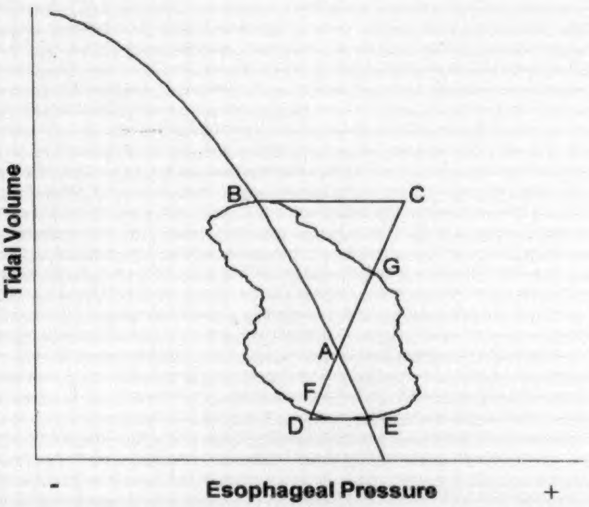

Figure 2-2. Modified Campbell diagram: A schematic of an esophageal pressure-volume (P-V) loop demonstrating partitioning of the components of muscular work of breathing during exercise. Line BE indicates the lung compliance curve within the present P-V loop. Line DC indicates the estimated chest wall compliance curve. Point A indicates the P-V relationship at functional residual capacity. Points B and C indicate the P-V relationship at EILV for lung and chest wall compliance, respectively. Points D and E indicate the P-V relationship at EELV for chest wall and lung compliance, respectively. Points F and G indicate the intersection of the dynamic P-V response with the chest wall compliance line for inspiration and expiration, respectively. Area ABCA indicates the inspiratory elastic work. Area AFBA indicates the inspiratory resistive work. Area ADEA indicates the expiratory elastic work. Area AGEA indicates the active expiratory resistive work.

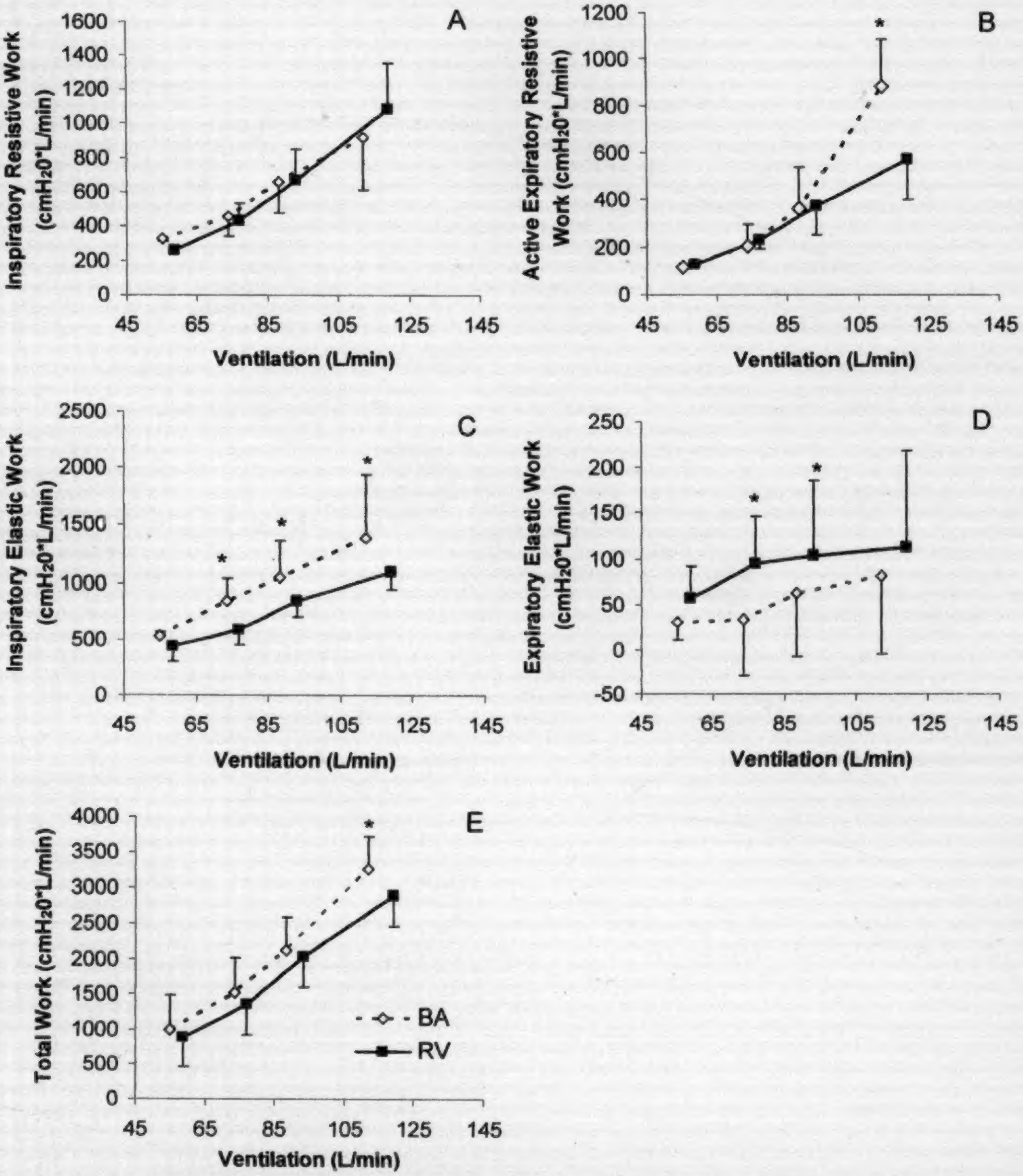

Figure 2-3. Work of breathing between the SCBA regulator (BA) and low resistance valve (RV) conditions at comparable ventilations. Inspiratory resistive (A), active expiratory resistive (B), inspiratory elastic (C), expiratory elastic (D), and total (E) work.

*significant difference between the BA and RV conditions, $p < 0.05$.

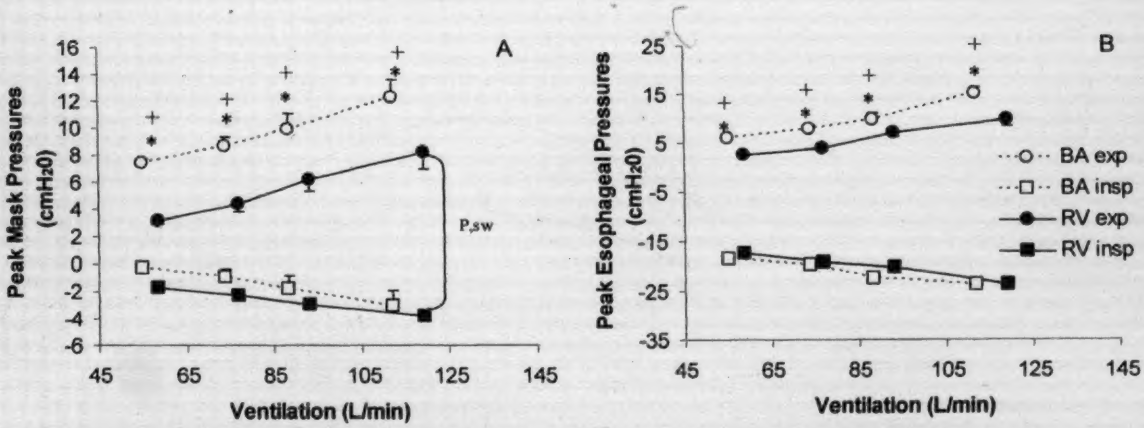

Figure 2-4. Peak mask (A) and esophageal (B) pressures during inspiration and expiration. P,sw = pressure swing (peak expiratory – peak inspiratory pressure), BA = SCBA regulator, RV = low resistance valve.

*significant difference between the BA and RV conditions for peak pressures, $p < 0.05$;

+significant difference between the BA and RV conditions for pressure swings, $p < 0.05$.

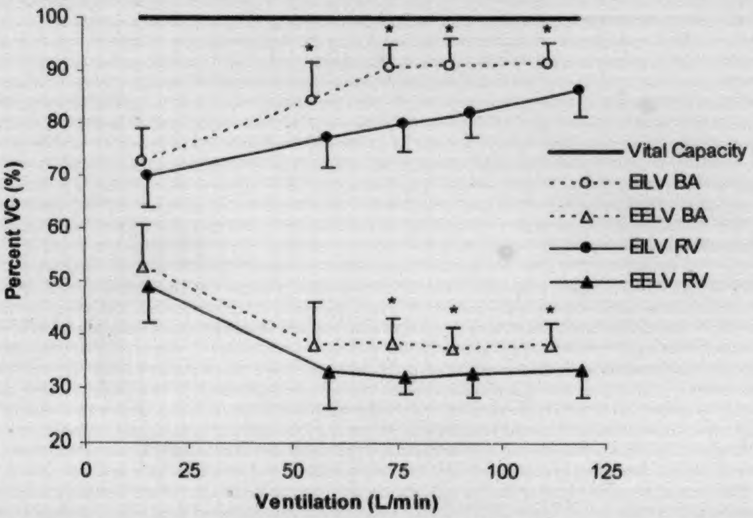

Figure 2-5. Lung volumes obtained at comparable ventilation rates throughout exercise. VC = vital capacity, EILV = end inspiratory lung volume, EELV = end expiratory lung volume, BA = SCBA regulator, RV = low resistance valve. *significant difference between the BA and RV conditions, $p < 0.05$.

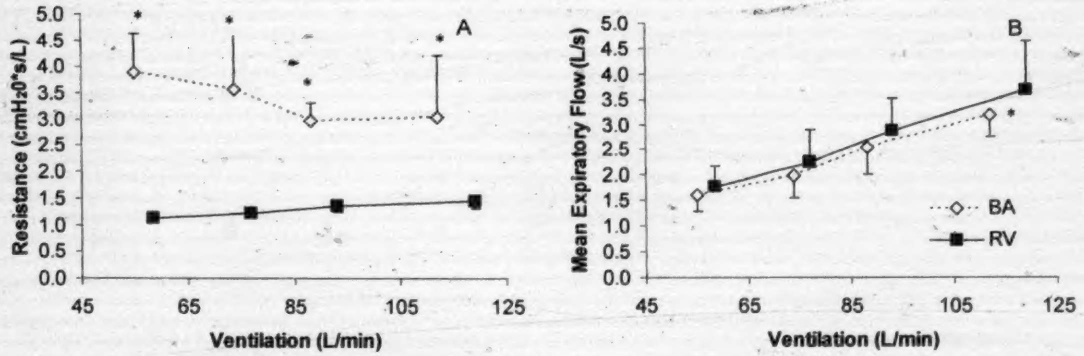

Figure 2-6. External expiratory breathing resistance (A) and mean expiratory flow rates (B). Breathing resistance was calculated as the mean mask pressure divided by the mean flow rate. BA = SCBA regulator, RV = low resistance valve. * significant difference between the BA and RV conditions, $p<0.05$.

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CHAPTER THREE

IMPAIRMENT OF EXERCISE VENTILATORY MECHANICS WITH THE SELF-CONTAINED BREATHING APPARATUS IS IMPROVED WITH HELIOX

3.1 INTRODUCTION

Fire protective equipment (FPE), including the self-contained breathing apparatus (SCBA), provides thermal and respiratory protection for firefighters in dangerous environments. However, the cost of this protection is reduced maximal exercise capacity resulting primarily from ventilatory limitation during heavy work (Dreger et al, 2006, Eves et al, 2005). This ventilatory limitation is in part due to an increased expiratory breathing resistance at heavy workloads (Eves et al, 2005), and to the accompanying increase in end-expiratory lung volume (EELV) caused primarily by the SCBA regulator (Butcher et al, 2006). Because of this increase in EELV, end-inspiratory lung volume (EILV) approaches total lung capacity (Butcher et al, 2006) which others have shown to constrain tidal volume (O'Donnell et al, 2001). The origin of the increased EELV is unknown, but would be explained if a mechanical flow limitation during expiration (Aliverti et al, 2002) were imposed by the SCBA regulator. Melissant et al (1998), have shown that mechanical flow limitation reduces maximal expiratory flow rates during spirometry, which would lead to the expectation of similar results with the SCBA. However, to our knowledge, there are no reports of the effects of the SCBA on resting pulmonary function.

The research completed in Chapter Two, in subjects using only the SCBA regulator during cycle ergometry in regular gym clothing, showed that the increased breathing resistance imposed by the SCBA regulator increases total respiratory muscle work of breathing (WOB) at ventilation rates at or above 112 $L \cdot min^{-1}$ (Butcher et al, 2006). The increase in total WOB is a result of increased expiratory resistive work to overcome the expiratory breathing resistance and an increased inspiratory elastic work from breathing at higher lung volumes (Butcher et al, 2006). In addition to the respiratory muscle work imposed by the regulator, the SCBA harness and cylinder may further increase WOB and impair pulmonary function due to the restriction imposed on the chest. Although this finding has not been reported with the SCBA, chest wall restriction by other means has been shown to reduce pulmonary function (Bygrave et al, 2004; Wang and Cerny, 2004). Therefore, the effects of FPE (including the SCBA) on pulmonary function and WOB are unknown.

Heliox (21% oxygen and 79% helium) is a low density gas mixture that, by reducing the turbulence to airflow at higher flow rates, reduces the mechanical constraint on ventilation, increases maximal flow rates, and decreases the resistive load in subjects breathing through a normal mouthpiece (Lambert, 1985; Wilson and Welch, 1980). Heliox has been shown to increase exercise capacity in subjects wearing FPE by increasing tidal volume and maximal ventilation while reducing expiratory mouth pressures (Eves et al, 2003a; 2003b). Heliox also appears to delay the onset of respiratory muscle fatigue with the SCBA (Eves et al, 2003b). These findings suggest that use of heliox with FPE and the SCBA should improve ventilatory mechanics and decrease the WOB during heavy exercise.

The aim of this research was to examine the effects of the SCBA and FPE on resting pulmonary function and exercise ventilatory mechanics, WOB, and respiratory muscle fatigue, and to examine the effects of heliox with the SCBA on the same variables. I hypothesized that the SCBA regulator would increase exercise WOB and respiratory muscle fatigue, and impair pulmonary function and ventilatory mechanics compared with a low resistance breathing valve, and that substituting helium for compressed air in the SCBA would, at least partially, reverse these effects.

3.2 METHODS

Subjects

Twelve healthy men participated in the study, which was approved by the University of Alberta Health Research Ethics Board. All subjects were experienced in the use of FPE and the SCBA during heavy exercise. Subject characteristics are presented in Table 3-1. Each subject provided written informed consent prior to enrolment.

Experimental design

A within-subject, repeated measures design was used to examine:

- the effects of the SCBA and firefighting clothing on vital capacity and resting static chest wall compliance. Experimental values were compared with values obtained when dressed in normal exercise clothing (t-shirt and shorts) without SCBA;
- resting pulmonary function during three breathing conditions (SCBA regulator with compressed air, BA-A; SCBA regulator with heliox, BA-H; low resistance breathing valve, RV); and,

- ventilatory mechanics during exercise in the three breathing conditions.

Baseline pulmonary function and chest wall compliance

Baseline pulmonary function and chest wall compliance were measured in two conditions: first, while the subject was seated upright and dressed in FPE including the SCBA (described below); and second, when the subject was dressed in normal exercise clothing (t-shirt and shorts) without the SCBA. Spirometry was performed using a dry-rolling seal spirometer (SensorMedics, Yorba Linda, CA) in accordance with standard procedures (American Thoracic Society, 1995) and compared to reported norms (Crapo et al, 1981). Chest wall compliance was measured after 2-3 practice sessions. An esophageal balloon was inserted (as described below) to measure esophageal pressure. Subjects breathed through a mouthpiece and plastic tube (2.2 cm ID) into the spirometer in order to measure lung volumes. At varying lung volumes between total lung capacity to residual volume, the tube was occluded so that when the subjects relaxed against the occlusion, esophageal pressure estimated the chest wall recoil pressure. After several occlusions across the range of lung volumes, the esophageal pressure and lung volume data points were plotted. Several spurious points indicating incomplete relaxation were removed from each plot. A polynomial trendline was used to create an estimate of the static chest wall compliance curve (Figure 3-1). Static resting chest wall compliance was calculated as a one-litre change in volume from functional residual capacity divided by the corresponding change in esophageal pressure.

Resting pulmonary function and exercise tests

Exercise tests were completed over 5 visits to the laboratory, which were separated by at least 48 hours. For all tests described below, subjects wore an ensemble of protective equipment including firefighting pants, jacket, gloves, anti-flash hood, helmet and SCBA (Scott 4.5; Scott Health and Safety, Monroe, NC) including backpack (harness and air cylinder) and facemask (AV 2000). During the BA-A and BA-H conditions, a Scott SCBA regulator (E-Z FLO) was also used. All above equipment met current safety standards and was consistent with duty gear used by Edmonton Fire-Rescue, a major urban fire department. During the RV condition, a low resistance Rudolph breathing valve (RV: 2700 Series, Hans Rudolph, Kansas City, MO) was mounted to the facemask as previously described (Butcher et al, 2006).

During the first visit, subjects were familiarized with the research techniques and underwent graded exercise testing on custom-built stairs (two steps, each 20.3 cm in height). A metronome was used to control stepping cadence. The graded exercise test began at 59 steps per minute and increased every two minutes by approximately 12 steps per minute up to volitional exhaustion. Expiratory gas was collected through a Plexiglas cone mounted to the SCBA regulator as previously described (Eves et al, 2002) and ducted to a metabolic cart (TrueOne Parvomedics, Salt Lake City, UT) in order to measure respiratory gases. During the second session, the subjects completed a full practice of the exercise protocol used in the three experimental trials.

The three experimental trials were completed on separate days and the order of the breathing conditions was randomized. Before each of the exercise trials, the subject completed maximal expiratory vital capacity maneuvers under the specified breathing condition. Resting pulmonary function was evaluated using the same spirometer and following the same procedures described above. Inspiratory maneuvers could not be performed with the SCBA since the inspired breath is drawn from the cylinder through high-pressure lines and the pressure-reducing regulators.

After performing spirometry, the subject completed three 10-minute bouts of constant cadence stepping exercise inside a body plethysmograph (described below). There was a 5-minute recovery period between bouts. The step rate for each subject was set as close as possible to 80% of the peak step rate attained during his graded exercise test. Data were collected in the tenth minute of each exercise period, and were subsequently reported as 10, 20 and 30-minute data points.

Exercise esophageal pressure, mask pressure, heart rate, and core temperature

All exercise pressure data were measured using differential pressure transducers (MP45 ± 50 cmH_2O, Validyne, Northridge, CA) connected to an amplifier (Model MC 1-3, Validyne, Northridge, CA), collected at 200 Hz with an automated digital chart recorder (PowerLab/8SP, ADInstruments, Castle Hill, Australia) and stored on a desktop computer. The transducers and associated tubing and connectors had a linear frequency response up to 5 Hz. Esophageal and mask pressure were measured continuously throughout exercise as previously described (Butcher et al, 2006). Esophageal pressure was measured with a 10 cm balloon catheter (Ackrad Laboratories Inc., Cranford, NJ), which was positioned according to standard procedure (Milic-Emili et al. 1964). Mask pressure was measured through a small port in the facemask. Peak inspiratory and expiratory pressures during tidal breathing were recorded. As well, pressure swings (peak inspiration to peak expiration) were calculated during the last minute of each 10 minute exercise bout. Heart rate was recorded every minute during exercise using telemetry

(Polar USA Inc., CT). Core temperature was measured by an ingestible, disposable capsule and recorded by telemetry using a VitalSense monitor (MiniMitter Inc, Bend, OR).

Exercise lung volumes

The custom-built body plethysmograph (body box) used in Chapter Two, was modified to increase the height to 2.46 m to allow stepping exercise. This body box was used to measure lung volume change during exercise as described in Chapter Two (Butcher et al. 2006). Briefly, a pressure transducer (MP45 ± 50 cmH_2O, Validyne, Northridge, CA) was connected to the body box so that changes in box pressure could be measured. In the RV condition, subjects inspired air ducted from the exterior of the box. In both the BA-A and BA-H conditions, subjects inspired air or heliox from the SCBA. In all conditions, expired gas was ducted to the exterior of the box so that the tidal volume or inspiratory capacity could be calculated from the change in box pressure. Tidal volume, respiratory rate, ventilation, duty cycle, and flow rates were calculated for each breath during the final minute of each bout and then averaged. Changes in EELV were estimated from measurements of inspiratory capacity (IC) during exercise. Assuming total lung capacity and vital capacity (VC) do not change with exercise (Stubbing et al, 1980), EELV was estimated by VC – IC. EILV was estimated by adding tidal volume to EELV obtained during exercise. Inspiratory reserve volume (IRV) was estimated by VC – EILV. Lung volumes were expressed as a percentage of VC.

Work of breathing

Similar to the protocol used in Chapter Two, and that of others (Yan et al, 1996), active muscular WOB was estimated by using Campbell diagrams as illustrated in Figure 3-1 (Roussos and Campbell, 1986). Dynamic lung compliance curves were created by using the pressure-volume relationship at the zero flow points at end inspiration and end expiration. The static chest wall compliance curve (described above) was plotted with the lung compliance curve. Data from two or three breaths recorded just prior to the 10 minute mark of each exercise bout were used to create pressure-volume loops. The individual dynamic pressure-volume loops were superimposed and partitioned into elastic and resistive components during both inspiration and expiration (Roussos and Campbell, 1986). As shown on Figure 3-1, area a-b-c-a = inspiratory elastic WOB, area a-f-b-a = inspiratory resistive WOB, area a-e-d-a = expiratory elastic WOB, area a-g-e-a = expiratory resistive WOB. It should be noted that the expiratory resistive work measured by this method comprises only the active work performed by the expiratory muscles to overcome airflow resistance, and not any expiratory resistive work that is recovered by the elastic recoil of the lung during expiration. The area of each component was measured using a polar planimeter (Keuffel and Esser, Germany). Breaths were selected as those that most closely matched the average tidal volume and peak esophageal pressures obtained for a given stage of exercise. Data for each component of WOB were summed to give total inspiratory, total expiratory, and total WOB and were expressed as work rate per minute.

Respiratory muscle strength

Pre- and post-exercise maximal inspiratory (MIP) and expiratory (MEP) mouth pressures were used to determine inspiratory and expiratory muscle strength, respectively. MIP and MEP were obtained by having the subject produce a maximal quasi-isometric inspiration/expiration through a mouthpiece attached to an occluded rigid tube, similar to the method of Black and Hyatt (1969). The tube was connected to a positive/negative pressure gauge (Cole Parmer Co, Stratford, CT) and a small leak (approximately 1 mm in diameter) prevented facial muscle pressure contribution (Black and Hyatt, 1969). The measurement of MIP began at residual volume and MEP at total lung capacity. MIP and MEP were not measured at functional residual capacity (FRC) because it was expected that different exercise intensities and gas mixtures would move EELV away from resting FRC in an inconsistent manner. Measurement from the extremes of lung volume ensured a standard starting position to minimize the effect of changes in inspiratory and expiratory muscle length on muscle force production.

Measurements of muscle strength were taken before exercise and again within four minutes following completion of the exercise protocol. Each maneuver was repeated until the two highest values were within 5 cmH_2O. The mean of these two values was recorded. The degree of respiratory muscle fatigue was estimated by the fatigue index (FI). For MEP, FI (%) = (MEP pre-exercise – MEP post-exercise) · 100 / MEP pre-exercise. A similar calculation was performed for MIP.

Statistical Analysis

All analyses were completed using Statistica version 6.1 (StatSoft Inc., Tulsa, OK). The RV was considered the control condition and BA-A and BA-H were the experimental conditions. For WOB, lung volume, ventilation, esophageal and mask pressure, heart rate, and core temperature data, a 3 (condition) x 3 (time; 10, 20, and 30 minutes of exercise) repeated measures ANOVA was used. To analyze MIP and MEP data, a 3 (condition) x 2 (pre and post) repeated measures ANOVA was used. Fatigue index and spirometry data in the three conditions were analyzed with a one-way repeated measures ANOVA. For comparisons of baseline and FPE condition chest wall compliance, a paired t-test was used. Alpha was set *a priori* at 0.05 for all analyses. Where appropriate, a Tukey's post hoc multiple comparisons analysis was used to determine between and within condition differences. Data were expressed as mean ± SD unless otherwise indicated.

Sample size calculation

In my first thesis study, I tested 12 healthy male subjects during cycling exercise and compared the WOB with the SCBA regulator compared to a low resistance breathing valve. Expiratory resistive work of breathing was higher with the SCBA (881 ± 359 vs. 572 ± 229 $cmH_2O \cdot L \cdot min^{-1}$ in the low resistance valve) (Butcher et al, 2006). Using an alpha level of 0.05 and a power of 0.8, it was estimated that 7 subjects were required to show a significant difference between the SCBA and a low resistance breathing valve.

Although no known study has reported changes in work of breathing in the SCBA with heliox, I can make some inferences based on Eves et al. (2003) and Butcher et al (2006). In Butcher et al (2006), I found a moderate ($r = 0.80$ $p<0.01$) correlation between peak mask pressure and expiratory resistive work at high work rates suggesting that peak mask pressure could be used as a surrogate for work of breathing. Eves et al (2003) compared peak expiratory mask pressures during submaximal exercise on a treadmill in 15 healthy male subjects breathing both room air and heliox with the SCBA. Peak mask pressures were 11 ± 1.2 cmH_2O on room air and 8 ± 0.7 cmH_2O on heliox. Using these values, an alpha of 0.05, and a power of 0.8, it is estimated that 3 subjects are required to demonstrate significant differences between room air and heliox while on the SCBA.

3.3 RESULTS

Baseline pulmonary function and chest wall compliance

The FPE (without the facepiece or SCBA regulator) decreased resting EELV (2.40 ± 0.49 vs. 2.68 ± 0.48 L) and chest wall compliance (0.177 ± 0.70 vs. 0.216 ± 0.062 $L \cdot cmH_2O^{-1}$) compared with t-shirt and shorts ($p<0.05$). Table 3-2 shows resting pulmonary function results. Forced vital capacity (FVC) was significantly lower ($p<0.05$) in all three experimental conditions than the baseline value presented in Table 3-1, however, FVC was not different between conditions (Table 3-2). The BA-A decreased forced expiratory volume in one second (FEV_1), FEV_1/FVC and peak expiratory flow rates (PEF) compared with the RV. Mid expiratory flow rates were unaffected by the BA-A compared to the RV. Breathing heliox increased FEV_1, FEV_1/FVC, FEF_{50}, and PEF compared with both BA-A and RV. Maximal expiratory flow volume curves for one subject under the all three conditions are presented in Figure 3-2.

Work of breathing

Total expiratory WOB (Figure 3-3a) was significantly increased in the BA-A, but not the BA-H, compared with the RV after 10 and 30 minutes of exercise. Heliox significantly increased expiratory elastic WOB (Figure 3-3b) compared to the BA-A condition but this was significant only after 30 minutes. The BA-A increased expiratory resistive WOB (Figure 3-3c) during all three exercise bouts. Total inspiratory WOB (Figure 3-3d) was increased in the BA-A compared with the RV after 30 minutes, however; was decreased with the BA-H compared to the BA-A at 20 and 30 minutes. These changes were the result of a greater inspiratory elastic WOB (Figure 3-3e) in the BA-A compared with the RV at 30 minutes, a lower inspiratory elastic WOB in the BA-H compared with the BA-A across all three bouts, and no significant differences between groups for inspiratory resistive WOB (Figure 3-3f).

The net effect of the differences observed in the four components of WOB was a significant increase in total WOB (Figure 3-4a) in the BA-A compared with the RV only when ventilation rates exceeded 100 $L \cdot min^{-1}$. Compared to the BA-A, helium decreased total WOB during exercise. WOB in the BA-H condition was similar to the RV condition.

Exercise pressures and flow rates

Table 3-3 shows the results of the analysis of esophageal pressure, mask pressure, and respiratory flow rates. There were no significant differences in inspiratory or expiratory flow rates for any of the three conditions. There were no differences in peak inspiratory esophageal pressure between the BA-A and RV, however peak expiratory esophageal pressure was always significantly higher during exercise with the BA-A. Heliox decreased peak expiratory esophageal pressure compared with the BA-A after 30 minutes of exercise. Peak to peak esophageal pressure swings were always greater in the BA-A than the RV or the BA-H. Peak expiratory mask pressure and pressure swing were significantly higher in both SCBA conditions, but more so in the BA-A. When esophageal pressure swing was expressed as a value per minute (Figure 4b), there were significant increases in the BA-A compared to the RV only after 30 minutes, whereas the BA-H decreased pressure swings after 20 and 30 minutes, following a pattern similar to that observed with total WOB (Figure 3-4a).

Exercise lung volumes and physiological variables

Figure 3-5 shows the end-inspiratory and expiratory lung volumes during exercise. EELV was significantly increased with the BA-A compared with the RV at 30 minutes while EILV was similarly increased at both 20 and 30 minutes. Breathing heliox resulted in significantly lower exercise lung volumes than were observed with compressed air. Table 4 demonstrates that there were no differences between conditions for core temperature, ventilation, tidal volume, respiratory rate, or heart rate; however, core temperature, ventilation, respiratory rate and heart rate all increased systematically throughout exercise. The BA-A resulted in a significantly lower duty cycle than the RV only after 10 minutes of exercise.

Respiratory muscle strength

Table 3-5 shows that after 30 minutes of exercise, MIP and MEP were significantly decreased from the pre-exercise values only in the BA-A condition. Similarly, fatigue indices were significantly increased only in the BA-A condition.

3.4 DISCUSSION

The effect of the FPE on baseline pulmonary function and chest wall compliance

The fire protective clothing, SCBA harness and air cylinder all contribute to a strapping force to the chest wall, which had a significant effect on resting ventilatory mechanics. This strapping effect decreased vital capacity (4%) and chest wall compliance (20%) causing resting EELV to decrease (10%) compared to baseline (t-shirt and shorts). For a given change in tidal volume, the reduction in chest wall compliance would increase the inspiratory elastic WOB (Roussos and Campbell, 1986). For this reason, my previous method of measuring WOB by estimating chest wall compliance in t-shirt and shorts (Chapter Two) would have been inaccurate when the extra weight and restriction of the SCBA tank and harness was imposed. Therefore, the measured chest wall compliance curve at rest with FPE, the SCBA harness, and the air cylinder was used as an estimate of the dynamic chest wall compliance during exercise on the Campbell diagrams (Roussos and Campbell, 1986).

The effect of the SCBA regulator on resting and exercise ventilatory mechanics

During resting spirometry, we observed that the primary effect of the SCBA regulator compared to the low resistance valve was to reduce PEF (15%) and FEV_1 (4%) without a significant change in mid expiratory flow rates or FVC; an effect which may be due to an expiratory flow limitation (Melissant et al, 1998). The presence of an expiratory flow limitation is a common cause of increases in lung volumes in patients with intrathoracic airway obstruction and in obesity (Johnson et al. 1999). I have shown previously (Chapter Two) and in this study (Figure 3-5) that the SCBA regulator increases EELV compared to the low resistance valve; however, the mechanisms behind this increase are unknown. Although we did not specifically address this question, we believe that an expiratory flow limitation is not likely responsible for the increased lung volumes with the SCBA. As the SCBA did not reduce maximal mid-expiratory flow rate during resting spirometry compared with RV and there were no differences in exercise expiratory flow rates, we believe a flow limitation with the SCBA was unlikely. In order to address this possibility, further study using methods to specifically examine expiratory flow limitation is required.

During exercise, I demonstrated that, compared to a low resistance breathing valve, the SCBA increased total work of breathing (by 58%) after 30 minutes of exercise ($V_E = 105$ L·min^{-1} with BA-A), but not after either 10 or 20 minutes when ventilation was significantly lower (75 and 87 L·min^{-1} with the BA-A, respectively). These ventilation rates are consistent with the metabolic demands required during heavy firefighting work (between 82 ± 14 and 102 ± 14 L·min^{-1} depending on the task) (Holmer and Gavhed, 2007) indicating that occupational performance may be affected by increases in WOB with the SCBA. Overall, these results were in agreement with my previous work that demonstrated increases in total work of breathing with the SCBA regulator but only at ventilation rates of 112 L·min^{-1} or greater (Butcher et al, 2006). Total WOB was very similar to that obtained in the previous study (3406 and 3248 cmH$_2$O·L·min^{-1}, respectively).

In contrast to my previous study of graded exercise (Butcher et al, 2006), the overall work rate in the present study remained consistent throughout the protocol. The increase in minute ventilation was most likely due to the increase in metabolic requirement with high intensity exercise (West 2005) and the increase in core temperature during the protocol (Hayashi et al, 2006) from 37.6 to 38.9 C with BA-A (Table 3-4). The increase in core temperature and the corresponding rise in minute ventilation were similar in all three breathing conditions. However, the added effect of the SCBA regulator caused the total WOB to be greater with BA-A.

The increase in total WOB was due in part to increases in inspiratory muscle work (55%), combined with a smaller absolute, but greater relative increase (133%) in expiratory muscle work. The increases in inspiratory work resulted from greater inspiratory elastic work (79%), which can be explained by the higher EILV and EELV. The higher expiratory muscle work was a result of increased expiratory resistive work (228%).

The greater inspiratory and expiratory muscle WOB likely contributed to the development of inspiratory and expiratory muscle fatigue similar to that observed by Eves et al (2003b) after 30 minutes of treadmill exercise wearing FPE and the SCBA. Although we cannot determine the mechanisms of the reduced post exercise respiratory pressures, the fatigue that did occur is likely due to the increased respiratory muscle load (Babcock et al, 1995). Respiratory muscle fatigue may reduce respiratory muscle performance after intense bouts of exercise with the SCBA. Respiratory muscle fatigue, however, does not normally affect acute exercise performance at submaximal exercise intensities (Johnson et al, 1996; Sliwinski et al, 1996). Any occupational impact of respiratory muscle fatigue from using the SCBA remains to be determined.

The effect of heliox on ventilatory mechanics with the SCBA

I also studied the effects of breathing heliox with SCBA on ventilatory mechanics. The increased expiratory resistance with the SCBA (compressed air) is likely caused by the valves in the regulator, which promote more turbulent airflow. The density of helium is approximately one third that of nitrogen, with only slightly greater viscosity (Lambert, 1982). The important effect of the reduced density of heliox is to decrease flow resistance when flow is turbulent (Lambert, 1982), such as occurs during exercise (Wilson and Welch, 1980). Based on the fact that respiratory flow rate is proportional to respiratory pressure generation and inversely proportional to airflow resistance (West, 2005), reduced flow resistance would be expected to either increase flow rates for a given WOB, or to decrease the WOB needed to maintain a given flow rate.

The typical effect of heliox during exercise in normal exercise situations is to increase flow rate, tidal volume, and minute ventilation during heavy exercise and to maintain WOB for a given exercise intensity (Babb, 2001; 2002). In contrast, I found that substituting heliox for compressed air in the SCBA reduced expiratory resistive WOB, inspiratory elastic WOB, and total WOB, but did not increase exercise tidal volume, ventilation rate (Table 3-4), or expired flow rate (Table 3-3). It is unclear why the use of heliox with the SCBA does not increase ventilation; however, these results are consistent with Eves et al (2003b) who also found that heliox did not increase ventilation or tidal volume with the SCBA during submaximal exercise. It is possible that the added effect of the SCBA harness and gas cylinder inhibits tidal volume increases, thus preventing higher ventilation rates with heliox under this condition.

A second effect of substituting heliox with the SCBA was to reduce EILV and EELV, which corresponded to lowered inspiratory elastic and slightly increased expiratory elastic WOB compared with compressed air. If expiratory flow limitation was present with the SCBA, heliox would counter the flow limitation and decrease lung volumes similar to the effect observed in patients with obstructive lung disease (Eves et al, 2006). As mentioned previously, I do not believe that overt expiratory flow limitation is present with the SCBA. Heliox increases maximal expiratory flow at moderate to high lung volumes during spirometry (Schilder et al, 1963), and we observed this with the SCBA (Figure 3-5). These increased maximal flow rates, however, did not translate into increases in expiratory flow during exercise, and yet, EELV was still reduced. These findings further support my belief that a mechanical flow limitation was not present with the SCBA and that EELV during exercise was regulated by another factor, such as the change in expiratory resistance (McClaran et al, 1999). As recommended above, further study with techniques that more specifically measure expiratory flow limitation (such as the negative expiratory pressure technique or simultaneous plot of maximal and exercise flow volume loops) would be required to confirm our speculations (Johnson et al, 1999). Overall, my data suggest that resistive unloading was a more important effect of heliox with the SCBA than improved expiratory flow rate.

3.5 CONCLUSIONS

In conclusion, the SCBA significantly impaired ventilatory mechanics, pulmonary function, and respiratory muscle strength compared with a low resistance breathing valve due to the combination of increased expiratory breathing resistance and the increase in exercising lung volumes. The use of heliox with the SCBA reversed these effects by decreasing the resistive WOB during expiration and by reducing exercising lung volumes.

ENDNOTE:

A version of this chapter has been accepted for publication. Butcher SJ, Jones RL, Mayne JR, Hartley TC, Petersen SR. Impairment of exercise ventilatory mechanics with the self-contained breathing apparatus is improved with heliox. Eur J Appl Physiol January 2007

Table 3-1: Subject characteristics (n = 12) and baseline GXT and pulmonary function results.

Characteristic	Mean	SD	Min	Max
Age (years)	31.0	8.4	21	53
Height (cm)	179.2	8.0	165	190
Weight (kg)	81.6	7.7	70	92
BW-VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	39.4	5.1	32.9	48.5
FPE-VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	31.0	3.9	25.9	38.5
SRpeak ($steps \cdot min^{-1}$)	152.2	10.0	138	176
$V_E$peak ($L \cdot min^{-1}$)	120.3	13.4	92.8	139.6
FEV_1 (L)	4.3	0.4	3.5	4.9
FEV_1 (% predicted)	102.5	10.0	83.4	120.3
FVC (L)	5.7	0.7	4.9	7.4
FVC (% predicted)	104.4	11.2	91.6	122.7
FEV_1/FVC	0.76	0.06	0.63	0.85
PEF ($L \cdot s^{-1}$)	12.1	1.1	10.0	13.9

BW-VO_{2peak} = peak oxygen consumption relative to body weight, FPE-VO_{2peak} = peak oxygen consumption relative to body weight plus fire protective equipment weight, SRpeak = peak step rate on the graded exercise test, $V_E$peak = peak ventilation rate on the graded exercise test, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, PEF = peak expiratory flow rate.

Table 3-2. Pulmonary function results.

	RV	BA-A	BA-H
FEV_1 (L)	4.17 (0.41)	4.02* (0.43)	4.42*‡ (0.40)
FVC (L)	5.50 (0.73)	5.52 (0.72)	5.50 (0.71)
FEV_1/FVC	76.39 (7.56)	73.40* (7.68)	80.87*‡ (7.25)
PEF ($L \cdot s^{-1}$)	11.32 (1.58)	9.65* (1.68)	15.42*‡ (2.33)
FEF_{50} ($L \cdot s^{-1}$)	4.60 (1.32)	4.58 (1.20)	6.41*‡ (1.61)

Data are presented as mean (SD). RV = low resistance valve, BA-A = SCBA regulator with compressed air, BA-H = SCBA regulator with heliox, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, PEF = peak expiratory flow rate, FEF_{50} = mid expiratory flow rate. *significant difference from RV, $p<0.05$. ‡significant difference from BA-A, $p<0.05$.

Table 3-3. Esophageal pressure, mask pressure, and respiratory flow rates during the final minute of each exercise bout.

	10 minute			20 minute			30 minute		
	RV	BA-A	BA-H	RV	BA-A	BA-H	RV	BA-A	BA-H
Pes,pi	-13.83	-15.98	-13.83	-10.97	-14.02	-10.20‡	-11.11	-13.28	-9.66‡
(cmH_2O)	(4.11)	(3.63)	(2.68)	(4.50)	(3.98)	(3.52)	(5.10)	(3.60)	(3.26)
Pes,pe	6.14	7.95*	6.59	7.23	9.28*	7.99	7.76	11.23*	8.22‡
(cmH_2O)	(1.97)	(2.29)	(1.68)	(1.93)	(2.13)	(2.24)	(2.33)	(3.24)	(2.28)
Pes,sw	19.97	23.93*	20.42‡	18.21	23.23*	18.19‡	18.87	24.51*	17.85‡
(cmH_2O)	(3.44)	(4.36)	(2.89)	(4.15)	(5.25)	(3.63)	(5.24)	(6.18)	(3.81)
Pm,pi	-1.75	-1.38	-1.18	-2.94	-1.44	-1.42	-3.16	-2.92	-1.71
(cmH_2O)	(2.19)	(0.71)	(0.30)	(0.63)	(0.71)	(0.42)	(0.69)	(4.70)	(0.49)
Pm,pe	2.44	6.46*	5.80*‡	2.80	6.69*	5.94*‡	3.35	7.41*	6.10*‡
(cmH_2O)	(0.53)	(0.40)	(0.21)	(0.61)	(0.43)	(0.23)	(0.90)	(0.83)	(0.31)
Pm,sw	5.12	7.84*	6.98*‡	5.74	8.13*	7.36*‡	6.50	9.01*	7.81*‡
(cmH_2O)	(0.96)	(0.97)	(0.40)	(1.17)	(0.99)	(0.49)	(1.42)	(1.23)	(0.49)
$\dot{V}$,pi	4.85	5.11	4.95	5.40	6.32	5.77	8.52	6.97	7.14
($L \cdot s^{-1}$)	(1.54)	(1.45)	(1.08)	(1.83)	(2.04)	(1.10)	(7.71)	(1.82)	(2.51)
$\dot{V}$,pe	4.36	4.35	4.11	4.73	4.95	4.59	4.69	5.61	5.57
($L \cdot s^{-1}$)	(0.90)	(0.96)	(0.84)	(1.10)	(1.15)	(1.00)	(1.25)	(1.35)	(1.00)

Data are presented as mean (SD). RV = low resistance breathing valve, BA-A = SCBA regulator with compressed air, BA-H = SCBA regulator with heliox, Pes = esophageal pressure, Pm = mask pressure, $\dot{V}$ = flow rate, pi = peak inspiratory, pe = peak expiratory, sw = peak to peak pressure swing. *significant difference from RV, $p<0.05$. ‡significant difference from BA-A, $p<0.05$. Values are mean (SD).

Table 3-4. Selected physiological variables measured during the final minute of each exercise bout.

	10 minute			20 minute			30 minute		
	RV	BA-A	BA-H	RV	BA-A	BA-H	RV	BA-A	BA-H
T_C (°C)	37.3 (0.3)	37.6 (0.5)	37.5 (0.4)	38.0 (0.3)	38.3 (0.4)	38.1 (0.4)	38.8 (0.3)	38.9 (0.5)	38.8 (0.4)
V_E ($L \cdot min^{-1}$)	80.4 (14.0)	74.5 (8.7)	72.8 (7.8)	89.3 (14.8)	86.5 (9.6)	82.7 (9.6)	100.8 (14.9)	104.9 (12.2)	101.4 (11.8)
V_T (L)	2.53 (0.44)	2.64 (0.59)	2.56 (0.61)	2.44 (0.45)	2.60 (0.62)	2.46 (0.65)	2.37 (0.45)	2.43 (0.67)	2.43 (0.62)
RR (breaths/ min)	32.0 (4.2)	29.0 (4.9)	29.2 (3.9)	37.3 (6.2)	34.5 (6.2)	34.9 (5.8)	43.4 (7.5)	45.5 (10.6)	43.7 (9.7)
T_I/T_{TOT}	0.47 (0.04)	0.42* (0.04)	0.44 (0.05)	0.46 (0.04)	0.42 (0.05)	0.43 (0.06)	0.46 (0.05)	0.42 (0.05)	0.44 (0.07)
HR (bpm)	162.5 (12.4)	162.4 (12.0)	160.3 (14.4)	177.8 (12.1)	178.5 (12.0)	176.4 (15.8)	188.8 (12.6)	189.0 (12.0)	187.8 (13.8)
HR (%max)	86.1 (6.6)	86.1 (7.0)	84.9 (7.9)	94.2 (6.8)	94.6 (7.0)	93.4 (8.4)	100.0 (6.7)	100.1 (6.4)	99.4 (7.0)

Data presented as mean (SD).*significant difference from RV, $p<0.05$. RV = low resistance breathing valve, BA-A = SCBA regulator with compressed air, BA-H = SCBA regulator with heliox, T_C = core temperature, V_E = minute ventilation, V_T = tidal volume, RR = respiratory rate, T_I/T_{TOT} = duty cycle, HR = heart rate.

Table 3-5. Respiratory muscle strength.

	RV	BA-A	BA-H
MIP pre (cmH_2O)	134.0	140.1	139.7
	(23.3)	(21.8)	(24.5)
MIP post (cmH_2O)	133.8	122.1*,[a]	141.8‡
	(22.8)	(15.8)	(25.4)
MIP-FI (%)	0.0	12.3*	-1.5‡
	(3.6)	(6.3)	(3.4)
MEP pre (cmH_2O)	197.3	191.3	195.3
	(61.5)	(55.5)	(65.2)
MEP post (cmH_2O)	186.1	162.1*,[a]	183.6‡
	(60.4)	(42.9)	(59.1)
MEP-FI (%)	5.5	14.0*	5.3‡
	(9.4)	(10.8)	(7.6)

Data presented as mean (SD). *significant difference from RV, $p<0.05$. ‡significant difference from BA-A, $p<0.05$. [a]significant difference from pre-exercise value, $p<0.05$. RV = low resistance breathing valve, BA-A = SCBA regulator with compressed air, BA-H = SCBA regulator with heliox, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure, FI = fatigue index.

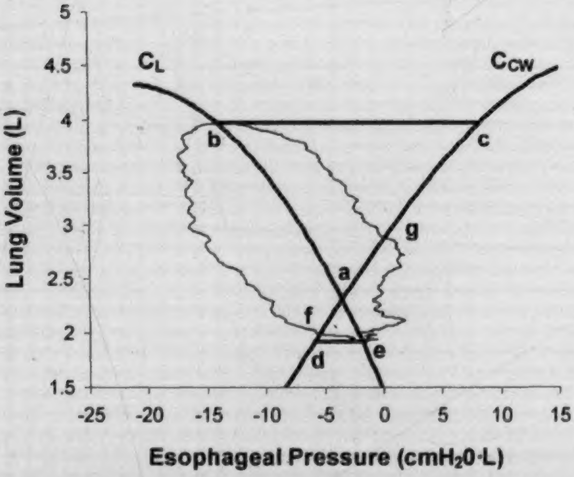

FIGURE 3-1. Example of a Campbell diagram. C_L = lung compliance curve, C_{CW} = chest wall compliance curve, area abca = inspiratory elastic work of breathing (WOB), area afba = inspiratory resistive WOB, area aeda = expiratory elastic WOB, area agea = expiratory resistive WOB.

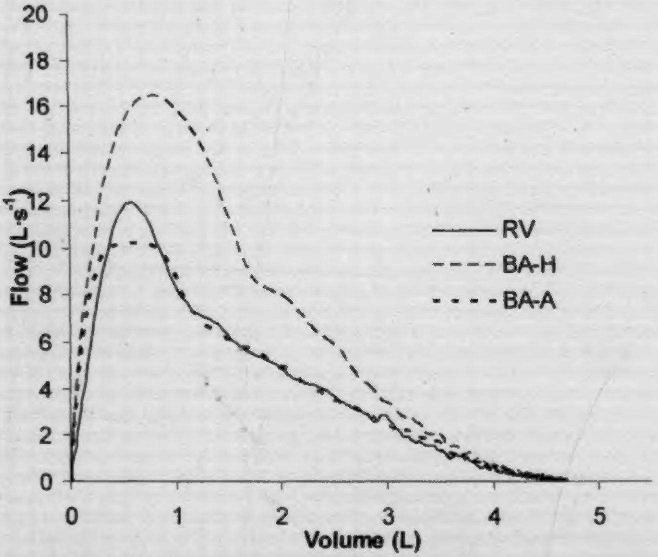

FIGURE 3-2. A representative example of the maximal expiratory flow volume curve in one subject for BA-A, BA-H, and RV. RV = low resistance breathing valve, BA-A = SCBA regulator with compressed air, BA-H = SCBA regulator with heliox.

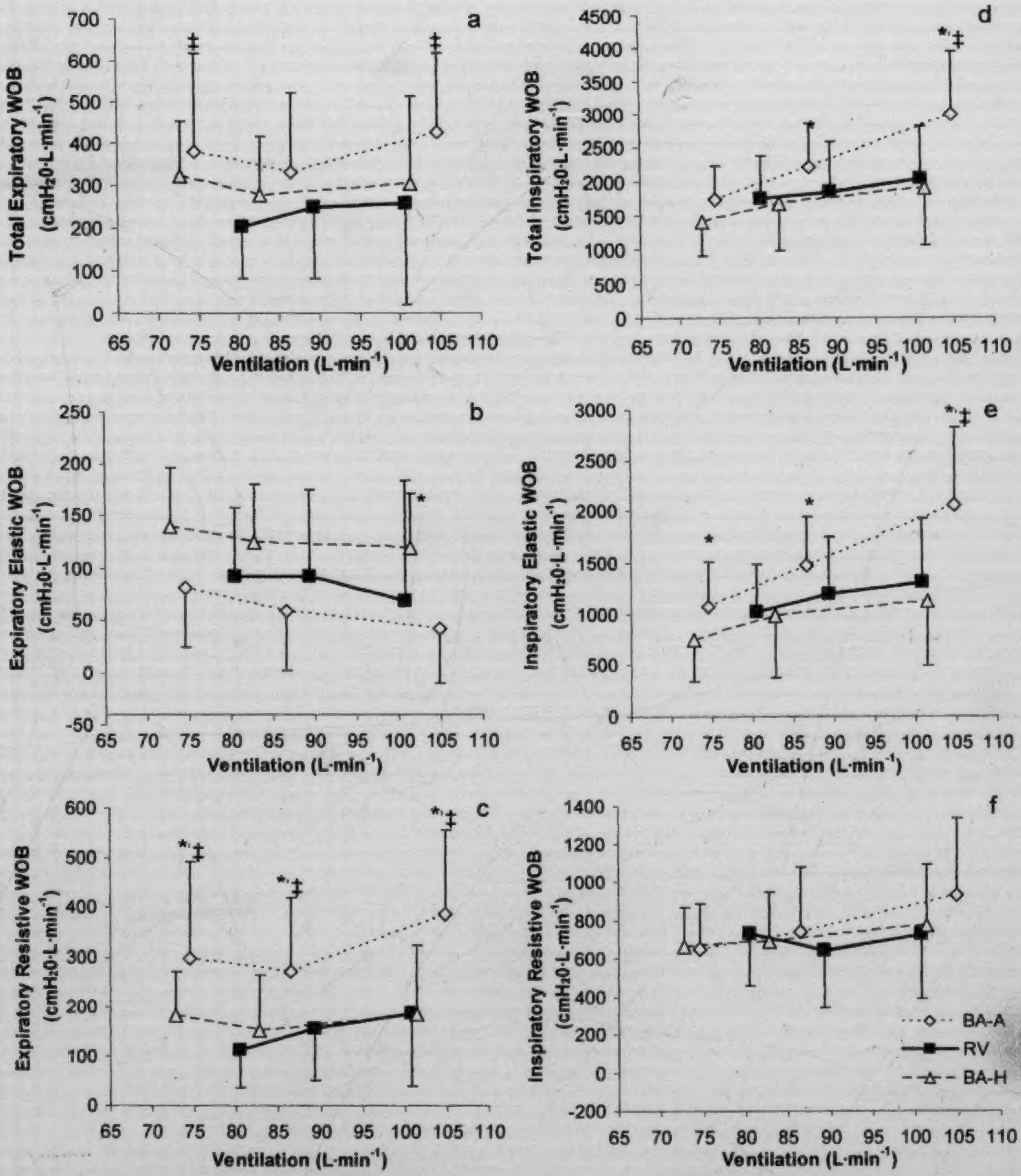

FIGURE 3-3. Inspiratory and expiratory work of breathing. Data represent values for minutes 10, 20, and 30. *significant difference from BA-H, p<0.05, ‡significant difference from RV, p<0.05. RV = low resistance breathing valve, BA-A = SCBA regulator with compressed air, BA-H = SCBA regulator with heliox.

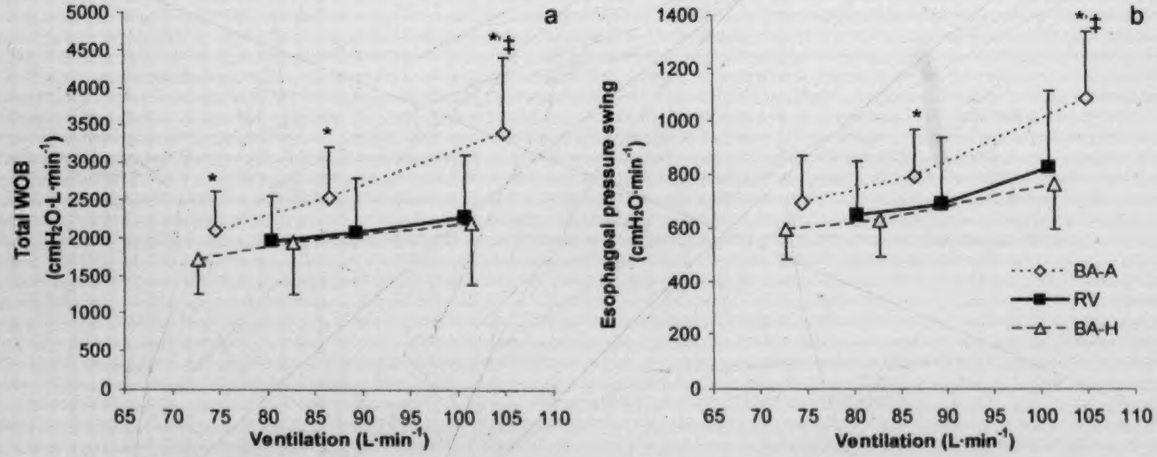

FIGURE 3-4. Total work of breathing and esophageal pressure swings. Data represent values for minutes 10, 20, and 30. *significant difference from BA-H, $p<0.05$, ‡significant difference from RV, $p<0.05$. RV = low resistance breathing valve, BA-A = SCBA regulator with compressed air, BA-H = SCBA regulator with heliox.

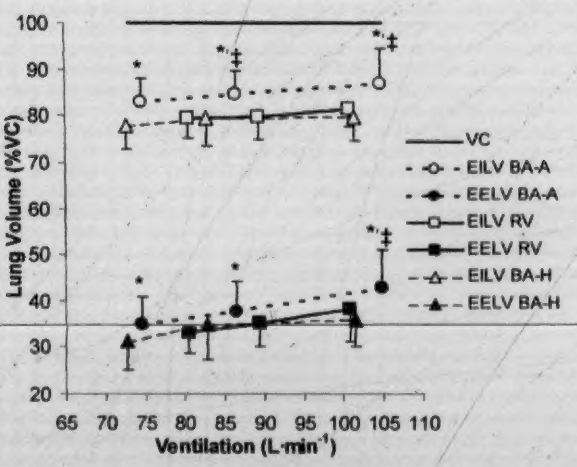

FIGURE 3-5. Lung volumes during exercise. Data represent values for minutes 10, 20, and 30. VC = vital capacity, EILV = end inspiratory lung volume, EELV = end expiratory lung volume, RV = low resistance breathing valve, BA-A = SCBA regulator with compressed air, BA-H = SCBA regulator with heliox. *significant difference from BA-H, $p<0.05$, ‡significant difference from RV, $p<0.05$.

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CHAPTER FOUR

INTERACTION BETWEEN VENTILATORY CONSTRAINT AND CONTRACTILE MUSCLE FATIGUE DURING EXERCISE IN PATIENTS WITH COPD

4.1 INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) often exhibit severe dyspnea and exercise intolerance, even with low levels of activity. Determining the source of exercise limitation in patients with COPD has been a topic of great interest recently (O'Donnell et al, 2001a; 2001b; Saey et al, 2003; Casaburi, 2003) and may be important for optimizing the benefit obtained from exercise rehabilitation. Traditionally, an inability to increase ventilation (V_E) due to expiratory flow limitation, and the consequent dynamic hyperinflation, was thought to be the primary exercise-limiting factor in most COPD patients (Casaburi, 2003). Certainly, estimates of ventilatory limitation (such as dynamic hyperinflation) correlate closely with reduced maximal and submaximal exercise tolerance (O'Donnell et al, 2001b; Marin et al, 2001; Medoff et al, 1998). Dynamic hyperinflation is also associated with increasing dyspnea and an increased work of breathing (Sliwinski et al, 1998; Diaz et al, 2000), and therapies that decrease dynamic hyperinflation such as bronchodilators (O'Donnell et al, 2006) and supplemental oxygen (O'Donnell et al, 2001a) significantly improve exercise tolerance. Heliox (79% helium, 21% oxygen), through it's effect of increasing expiratory flow rate (Lambert, 1985), has also been shown to delay dynamic hyperinflation and increase exercise tolerance time in COPD patients (Eves et al, 2006; Palange et al, 2004; Richardson et al, 1999). These findings support the traditional view of the importance of ventilatory limitation to exercise in COPD patients.

The systemic consequences of COPD on skeletal muscle strength (Yende et al, 2006; Bernard et al, 1998), morphology (Montes De Oca et al, 2006) oxygen delivery (Simon et al, 2001), and fatigue (Mador et al, 2003) have also been recognized as playing a significant role in decreased exercise tolerance, at least in some COPD patients. In fact, quadriceps muscle fatigue is greater in COPD patients after cycling exercise compared to healthy age-matched adults (Mador et al, 2003) and this may be an important exercise-limiting factor (Saey et al, 2003). Saey et al (2003) studied the effects of the bronchodilator ipratropium bromide on exercise tolerance and quadriceps contractile fatigue; hypothesizing that a positive response to the bronchodilator would occur only in patients who did not have exercise-induced quadriceps fatigue. They found that

50% of patients developed significant levels of quadriceps fatigue and did not increase exercise tolerance after bronchodilation despite a 12 ± 18% improvement in FEV_1. The other 50% who did not have prebronchodilator quadriceps muscle fatigue increased exercise tolerance after ipratropium bromide but this eventually caused them to develop muscle fatigue as well. This finding suggests that baseline exercise, in the latter group, was initially limited by ventilatory limitation. However, due to the wide degree of variability in individual subject response as well as the marginal clinical significance of the increase in FEV_1 with the bronchodilator (Pellegrino et al, 2005), it is unclear whether the bronchodilator used by Saey et al (2003) successfully relieved ventilatory limitation in all subjects. Perhaps the use of heliox to delay dynamic hyperinflation (Palange et al, 2004) would be more successful in relieving ventilatory constraints in all subjects.

Although Saey and colleagues (2003) showed muscle fatigue to be an important limiting factor during exercise in COPD, they did not report measures of ventilatory limitation. Therefore, it is unknown if their patients with muscle fatigue were also ventilatory limited during exercise, and if there was a relationship between the degree of ventilatory and muscular limitations. If ventilatory constraint is more prevalent in COPD patients who do not fatigue their leg muscles, then improving ventilatory capacity should increase exercise tolerance, which could eventually lead to muscle fatigue and, perhaps, a better exercise training response. To my knowledge, the relationship between measures of ventilatory limitation and leg muscle fatigue has not been reported. A better understanding of this relationship would be useful for developing individualized pulmonary rehabilitation programs. Therefore, I studied this relationship and hypothesized that: 1) delaying ventilatory limitation with heliox would increase exercise tolerance, and consequently, leg muscle fatigue and 2) heliox would cause a greater increase in exercise tolerance in patients not limited by leg muscle fatigue compared to those limited by leg fatigue.

4.2 METHODS

Subjects

Eleven patients with COPD (Table 4-1) were recruited from the pulmonary rehabilitation program at the Centre for Lung Health, Edmonton, Alberta. All subjects had previously completed at least 8 weeks of exercise rehabilitation and had stable COPD at the time of the study. Patients who required the use of supplemental oxygen, or who had significant musculoskeletal or cardiovascular conditions were excluded. This study was approved by the

University of Alberta Health Research Ethics Board and all subjects provided their written consent.

Baseline pulmonary function

To confirm diagnosis and determine disease severity, each patient had a pulmonary function test within three months of the study (SensorMedics Vmax22, Yorba Linda, CA). Lung volumes were determined using a constant-volume body plethysmograph (6200 Autobox; SensorMedics). Spirometry and single breath diffusing capacity (D_LCO) were compared to the reported norms of Crapo et al (1981) and lung volumes were compared to those from Goldman and Becklake (1959). Maximal voluntary ventilation (MVV) was estimated by forced expiratory volume in one second (FEV_1) x 35 (Gandevia and Hugh-Jones, 1957).

Experimental design

Each subject completed four days of exercise testing that were separated by at least 48 hours. Upon arrival each day, subjects were transported to the pulmonary function laboratory, the cycle ergometer and the isokinetic dynamometer via wheelchair to reduce the effects of walking on fatigue. On the first day, subjects were familiarized with the protocol and performed a graded exercise test to symptom limitation (VO_{2peak}). A single-blinded, randomized, crossover design was employed such that on the second and third days, subjects performed constant work rate exercise at 80% VO_{2peak} (see below) to symptom limitation and breathed either room air (RA) or heliox (79% helium and 21% oxygen; HE). On the fourth day, another constant work rate trial was performed while breathing heliox, however; the test was stopped at the same time that the subject stopped on the RA test (isotime; ISO). The gas cylinders were hidden from view of each subject and each subject was asked to not speak during and for one minute after breathing each experimental gas to assist in subject blinding.

Graded exercise test (GXT)

The GXT to symptom limitation was performed on an electronically-braked cycle ergometer (SensorMedics Ergometrics 800S). Seat height was recorded and replicated for the remainder of the study. The work rate increment (mean 10.9 ± 3.0 $W \cdot min^{-1}$) was determined individually by the supervising physician and was increased each minute. Heart rate and rhythm were recorded using a single-lead ECG monitor (43200A monitor, Hewlett Packard, Palo Alto, CA). Oxygen saturation (SpO_2) was measured using pulse oximetry (Sat-Trak, SensorMedics). Expired gas was ducted into a calibrated metabolic cart (TrueOne, Parvomedics, Salt Lake City, UT) and metabolic measurements were averaged every thirty seconds. The highest 30 second VO_2 obtained on this test was accepted as VO_{2peak}. Selected peak exercise data are presented in Table 4-1.

Exercise measurements

After a five minute wash-in period on the gas used each day, spirometry was performed to American Thoracic Society (1995) standards using a bag-in-box system connected to a dry-rolling spirometer (Sensormedics, Yorba Linda, CA) similar to that used previously (Eves et al, 2006). The constant work rate cycle ergometry test during RA and HE was performed at 80% (mean 79.9 ± 3.9%) of the peak work rate obtained on the GXT and was stopped at symptom limitation. Pedal cadence was maintained between 50 and 70 rpm. Either RA or HE was inspired from a ~60L reservoir bag. Expired gas was ducted to the same metabolic cart used in the GXT, which was calibrated for the gas mixture used. Inspiratory capacity (IC) was measured using a bag-in-box system. A series of three-way valves permitted an easy transition between the two breathing circuits. Two IC maneuvers were performed at each measurement point. Total lung capacity was assumed to remain at the resting value and exercise lung volumes were calculated as follows. End-expiratory lung volume (EELV) = total lung capacity (TLC) – IC. End-inspiratory lung volume (EILV) = EELV + tidal volume (V_T). The degree of ventilatory constraint was assessed by V_E/MVV, V_T/IC, EELV, and EILV. Heart rate was recorded using telemetry (Polar USA Inc., CT). Symptoms of dyspnea and leg fatigue were recorded using a modified Borg 10 point visual analog scale (Noble et al, 1983). During exercise, data were recorded every two minutes and at the point of symptom limitation prior to exercise cessation. After each exercise trial, subjects were asked to identify the primary symptom limiting exercise (dyspnea, leg fatigue, or both).

Maximal voluntary isometric knee extensor contraction (MVIC), interpolated twitch technique (ITT), and vastus lateralis potentiated twitch (TwVL)

Prior to each exercise session and at 5, 10, and 20 minutes into recovery, right knee extension MVIC and TwVL were obtained. Each subject was seated on a System 3 isokinetic dynamometer (Biodex Medical Systems Inc. Shirley, NY) with the right thigh horizontal and the knee flexed to approximately 90°. Positioning was standardized between subjects and within trials. The subject was secured across the thigh and ankle with Velcro straps and held handgrips to stabilize the hips and upper body. Maximal isometric knee extension torque was averaged over approximately one second at peak torque and recorded during the MVIC maneuvers. After sufficient practice (to achieve reproducibility within 5%), each subject performed 5 MVIC maneuvers (30 seconds apart) and the highest value was recorded and used in the analysis. Subjects were provided with visual feedback of torque production and were encouraged to perform maximally.

Supramaximal muscle stimulation (Morton et al, 2005; Belanger and McComas, 1981) was applied over the right vastus lateralis motor point using a magnetic stimulator and parabolic coil (Magpro R30, Medtronic Inc.). The stimulation site was marked in permanent ink to enable the coil to be placed in the same location and orientation for each testing session. Electromyographic (EMG) responses (M-waves) were recorded via bipolar surface Ag-AgCl electrodes (Vermed Medical Inc., Bellows Falls, VT) placed over the belly of the right vastus lateralis muscle. EMG signals were pre-amplified 500-1000× and band-pass filtered at 10-3000 Hz (AMT-8, Bortec Biomedical Ltd, Calgary, AB). Torque and EMG data were recorded at 2000 Hz using a custom program (LabView, National Instruments) and stored on a computer for analysis. At the beginning of each subject's testing protocol, a recruitment curve was constructed from responses to 40 incremental stimuli. In all subjects, a maximal M-wave was obtained prior to reaching 100% of the stimulator's power output (mean 83.4 ± 9.6%). For the measurement of TwVL, the magnetic stimulator was set at 100% to evoke a supramaximal M-wave.

The ITT (Shield and Zhou, 2004) was performed on the last three MVIC maneuvers at each measurement point. As well, a resting potentiated twitch (TwVL) was obtained 1-2 seconds after each of the above MVIC maneuvers to determine the contractile properties of the vastus lateralis. Voluntary activation (VA) was calculated as 100 – (superimposed ITT/TwVL) x 100% (Shield and Zhou, 2004). The degree of contractile fatigue was measured as the percent change from baseline in TwVL torque at each of the three testing times during recovery. Contractile fatigue was deemed to have occurred if post exercise TwVL was equal to or less than 85% of baseline (Saey et al, 2003). Subjects were then divided into fatiguers (F) and non-fatiguers (NF) for the analysis (Table 4-1).

Statistical Analysis

A one-way repeated measures ANOVA was used to determine differences between the three constant load exercise trials for exercise measurements and muscle data for all subjects. Pulmonary function data and exercise tolerance time were analysed using paired t-tests for RA and HE. To examine the relationships between muscle, ventilatory, and exercise data, Pearson's correlation coefficients were used. A two (F, NF) times three (RA, HE, ISO) repeated measures

ANOVA was used for comparison of the exercise responses between the F and NF groups. Muscle strength and fatigue data were also analysed with a two (F, NF) times four (rest, 5, 10, and 20 minutes of recovery) repeated measures ANOVA. An unpaired t-test was used to compare the baseline subject characteristics (F vs. NF). Spirometry responses were analysed using a two (F, NF) times two (RA, HE) repeated measures ANOVA. Where significance was found in the ANOVA, a Tukey's HSD post hoc analysis was used to determine the individual group differences. An alpha value of <0.05 was considered significant for all analyses and post hoc tests. Data are presented as mean ± SD unless specified. All analyses were completed using Statistica version 6.1 (StatSoft Inc, Tulsa, OK).

Sample size calculation

The effect of heliox on high intensity exercise tolerance and ventilatory limitation in patients with COPD has been studied previously by Palange et al (2004). They found that exercise tolerance increased from 4.2 ± 2.0 minutes to 9.0 ± 4.5 minutes (Palange et al, 2004). Using these values, an alpha of 0.05 and a power of 0.80, it was estimated that 5 subjects were needed to demonstrate significant differences. In regards to the attainment of leg fatigue, Saey et al (2003) studied 18 patients with COPD and found that 9 of the 18 exhibited leg muscle fatigue after cycling exercise. They found that those who fatigued more dropped force to 64 ± 26% of resting, whereas those who fatigued less declined to only 98 ± 10% of resting. Using these values, an alpha of 0.05 and a power of 0.80, it was estimated that 4 subjects per group were needed in order to distinguish patients who fatigued and those who did not.

4.3 RESULTS

Comparisons among all subjects

Resting pulmonary function, ventilation, and lung volumes

Table 4-2 shows the pulmonary function and ventilation data for both the RA and HE tests for all subjects. Heliox increased FEV_1 by 11 ± 13% and PEF by 25 ± 16% ($p<0.05$) with no change in FVC, EELV, EILV, or minute ventilation.

Exercise, ventilation, and fatigue data

Individual exercise tolerance times and 5 minute TwVL scores are presented in Figure 4-1 for all subjects. Heliox increased exercise tolerance time by 53.1 ± 40.5% resulting in a 14.5 ± 11.8% decrease in 5 minute TwVL ($p<0.05$) in all subjects. Selected mean exercise data are presented in Table 4-3 and Figure 4-2. Heliox also significantly decreased MVIC, but did not change

V_E/MVV or V_T/IC at symptom limitation. There were no differences in ventilation data, lung volumes, or perceptions of dyspnea and leg fatigue at symptom limitation. At isotime, compared to the RA test, heliox increased oxygen saturation, IRV, and, V_T/IC, and decreased EELV and symptoms of dyspnea and leg fatigue, but maintained MVIC and 5 minute TwVL to similar levels as the RA test. There were no differences in VA across the three trials.

Correlates

Change in exercise time between the RA and HE tests was correlated with the 5 minute TwVL during room air breathing ($r = 0.79$, $p<0.05$), change in FEV_1 ($r = 0.70$, $p<0.05$) and room air EILV ($r = 0.68$, $p<0.05$). As well, 5 minute TwVL was correlated with EELV ($r = -0.77$, $p<0.05$) and change in EELV from rest to peak exercise ($r = -0.66$, $p<0.05$). The results indicate that patients with the least amount of muscle fatigue were more ventilatory limited and responded to breathing heliox to a greater degree. There were no other significant correlations between exercise time, pulmonary function, muscle fatigue, ventilatory constraint, or perceptions of dyspnea and leg fatigue.

Comparisons between F and NF

Baseline characteristics

Table 4-1 shows the baseline pulmonary function, muscle strength, and GXT results for each group. Compared to F, the NF group had poorer lung function, lower values for quadriceps isometric torque, peak exercise ventilation, and oxygen saturation, and a greater level of ventilatory limitation (higher V_E/MVV) during the GXT. There was a trend for a higher proportion of subjects who perceived dyspnea as the primary reason for stopping exercise in the NF; whereas the F tended to more frequently report leg fatigue as the limiting symptom.

Exercise tolerance and muscle fatigue

Figure 4-3 shows the changes in 5 minute TwVL and exercise time with HE in both F and NF. Both groups demonstrated similar exercise tolerance times on the RA test, however; the F achieved a significantly greater level of vastus lateralis muscle fatigue than the NF. With the HE test, only the NF group increased exercise tolerance time, which resulted in a significant increase in the level of muscle fatigue (5 minute TwVL) to a similar level as the F. For F subjects, HE failed to increase either exercise time or the level of muscle fatigue. Figure 4-4 shows the data for the MVIC maneuvers and TwVL at all three post exercise testing periods in both the RA and

HE tests. MVIC and TwVL followed a similar pattern of change for F and NF during both RA and HE trials, however; the magnitude of the changes was greater for TwVL.

Ventilatory constraint, metabolic measurements, and perceptual variables

During pre-exercise spirometry, the NF and F had a similar increase in FEV_1 with heliox (8.3 ± 11.3% and 16.1 ± 13.6%). During exercise, as shown in Figure 4-5 and Table 4-4, the NF demonstrated greater ventilatory constraint due to greater exercise lung volumes, V_E/MVV, and symptoms of both dyspnea and leg fatigue than the F subjects. As well, NF had a lower V_E, V_T, VO_2, and VCO_2 on both the RA and HE tests. There were no differences between groups or gas mixtures for respiratory rate or heart rate. Both groups decreased exercise lung volumes at isotime with heliox to a similar degree. Compared with the RA test, the isotime helium test in the NF group resulted in decreased V_T/IC, V_E/MVV, dyspnea and leg fatigue symptoms, and increased V_T and oxygen saturation.

4.4 DISCUSSION

The effect of changes in ventilatory constraint on leg muscle fatigue

The main finding from this study was that high intensity cycling exercise time increased with heliox, resulting in greater vastus lateralis fatigue in patients with COPD. In addition, this response was most pronounced in patients with less initial leg fatigue (NF group), suggesting that those patients were limited by mechanisms other than leg fatigue. Because the NF group exhibited a greater degree of ventilatory constraint, they were more likely ventilatory limited. Furthermore, the F group had greater leg muscle fatigue after exercise while breathing room air and did not significantly increase exercise tolerance time with heliox despite reduced dynamic hyperinflation. These results support my hypotheses and suggest that the presence of a ventilatory limitation during cycling exercise impairs exercise prior to the attainment of a significant level of leg muscle fatigue. By delaying this ventilatory limitation with heliox, exercise capacity increases, which eventually leads to greater levels of leg muscle fatigue.

These results support the findings of Saey and colleagues (2003) who examined the effect of ipratropium bromide on exercise tolerance and quadriceps muscle fatigue using a similar measure of contractile quadriceps fatigue (85% of pre-exercise potentiated twitch at 10 minutes into recovery). These authors demonstrated that patients who were classified as NF after 80% constant work rate cycling increased exercise tolerance (by 92%) and exhibited greater muscle fatigue (by 15%) with ipratropium. These changes were similar in magnitude to the changes observed in the present study using heliox (77 ± 26% increase in exercise tolerance in NF and 20 ± 8% increase in muscle fatigue) despite the fact that our subjects had less severe COPD (FEV_1 52% vs 38%, respectively).

Interestingly, one of my subjects, classified as a fatiguer (5 minute TwVL = 82%), increased exercise tolerance by 43% with heliox. This subject also demonstrated ventilatory constraint after the room air test (V_T/IC = 95% and EILV = 98% of TLC). The increase in exercise time with heliox in this subject resulted in a 14% increase in vastus lateralis fatigue, which suggests that the cut-off for defining F and NF at a TwVL of 85% was too high and that this patient was misclassified. I do not believe this to be true, as one other subject in the F group attained a similar TwVL (82%), but did not increase exercise tolerance or level of muscle fatigue with helium. Alternatively, I suspect that the subject in the F group who increased exercise tolerance with helium was actually more limited by ventilatory constraint than by the level of muscle fatigue. An important implication here is that a TwVL < 85% of the baseline value does not necessarily indicate that task failure (exercise limitation) will occur (Hunter et al 2004). Therefore, it is possible for those reaching a certain level of muscle fatigue to attain a greater exercise tolerance with heliox if they are also ventilatory limited. In fact, most of the subjects in the NF group decreased TwVL to some degree 5 minutes into recovery and still were able to increase exercise tolerance with heliox. I demonstrated a significant negative correlation between change in exercise time and 5 minute TwVL across the entire subject sample. This correlation supports my view and that of others (Saey et al, 2003) that the occurrence of fatigue does not directly indicate imminent exercise cessation, but rather that greater levels of muscle fatigue predict a reduced change in exercise time with treatment of the ventilatory constraint.

Mechanisms of exercise limitation

This study examined the relative contributions of ventilatory constraint and peripheral muscle fatigue to exercise limitation in patients with COPD. Traditionally, ventilatory limitation occurs when peak exercise ventilation approaches maximal ventilatory capacity (ie. V_E/MVV > 90%). Problems with this approach have been documented and it may be more appropriate to express ventilatory limitation in terms of exercise lung volumes (O'Donnell 2001c). The physiologic hallmark of COPD is expiratory flow limitation, which causes dynamic hyperinflation when ventilation increases. Tracking the change in EELV can give a sensitive and reliable indicator of dynamic hyperinflation (Yan et al 1997). The maximal constraint on ventilation, however, occurs when EILV approaches TLC, in the presence of dynamic hyperinflation. O'Donnell et al (2001) found that many patients with COPD reached an EILV of approximately 94% of TLC (termed 'minimal inspiratory reserve volume'), indicating a constraint on tidal volume from below (an increased EELV) and above (low IRV) (O'Donnell et al, 2001). My results support the findings of O'Donnell since six out of our seven NF reached an EILV greater than or equal to 94% of TLC at end exercise on the RA test, whereas only one patient in the F group reached a similar level of ventilatory constraint. This one patient, however, was the same one discussed above who did increase exercise tolerance and, as such, was likely more ventilatory limited. On the HE test, all NF increased EILV to at least 94% indicating that ventilatory constraint was still an important mechanism limiting exercise during heliox breathing, despite an increase in muscle fatigue. Therefore, an EILV of 94% appears to be an appropriate indicator of ventilatory constraint in our patients.

Contractile leg fatigue has previously been used as an indicator of peripheral muscle limitation in patients with COPD (Saey et al 2003). Patients with COPD tend to exhibit greater levels of leg fatigue than age-matched healthy controls (Mador et al 2003); however, the mechanisms behind the increased fatigue remain unclear. Decreased muscle strength and endurance can be considered prime candidates; however, we observed that baseline voluntary leg strength was actually lower in the NF than the F group. Additionally, the greater level of muscle fatigue observed after room air exercise in the F group could potentially be explained by the fact that the F group exercised at a greater absolute work rate than the NF group; however, there was no association between work rate intensity and level of muscle fatigue ($r^2 = - 0.097$). This finding indicates that the level of fatigue incurred by each patient is not dependent upon absolute work rate. This suggestion is supported by the fact that patients with COPD usually have a lower maximal work rate, but a higher degree of fatigue (Mador et al 2003). Another explanation for the greater level of muscle fatigue in patients with COPD is that they tend to have a greater proportion of Type IIb muscle fibres, which may account for the greater level of fatigue compared to healthy older adults (Pereira et al, 2004). In comparing NF with F, however, Saey and colleagues (2005) found no differences in muscle fibre type, but there was an increased reliance on anaerobic metabolism in F. An alternative explanation is that leg muscle fatigue is brought on by inadequate blood flow to leg muscles due to increased work of breathing and the development of respiratory muscle fatigue (Romer et al 2006; Harms et al 1998). Simon et al (2001) demonstrated that some patients with COPD exhibit a plateau in leg oxygen consumption despite increasing whole body oxygen consumption with increased work rates. They suggested that increased respiratory muscle work may have caused a redistribution of cardiac output to the respiratory muscles (Simon et al 2001) similar to that observed in healthy subjects (Harms et al 1998). My protocol was not designed to assess this issue and we did not measure work of breathing or blood flow distribution in our study. Therefore, I cannot determine if this mechanism played a role in the changes in muscle fatigue observed. It is apparent, however, that relief of ventilatory constraint in F did not increase exercise tolerance nor alter the level of muscle fatigue, and that F, as a group, were likely limited by leg muscle performance.

Mechanisms of increased exercise tolerance with heliox

Heliox in my study had a similar effect on FEV_1 as did ipratropium in Saey and colleagues' (2003) study (increased by 11% vs. 12%, respectively); however, despite a variable individual response in FEV_1 (a standard deviation of 13%), I documented a consistent effect of improved lung volumes with heliox. There was no significant difference in the change in FEV_1 with heliox between the F and NF (16% vs. 8% increase, respectively). These data suggest that a lack of change in FEV_1 with heliox was not responsible for subjects in the F group not increasing exercise tolerance. These data confirm previous reports (O'Donnell et al, 1999) that increases in FEV_1 are not always associated with improved exercise tolerance in individual subjects.

In support of Palange et al (2004), the main effect of heliox was to reduce dynamic hyperinflation and increase exercise tolerance during cycling exercise in patients with COPD. Palange et al (2004) found that increased exercise tolerance with heliox was associated with both reduced dynamic hyperinflation and increased peak exercise V_E. In contrast, I did not observe a significant increase in the peak exercise V_E rate with heliox. This finding may be due to the fact that my subjects responded to heliox to a lesser degree than those studied by Palange and colleagues. Despite a similar change in FEV_1 with heliox, my subjects (NF and F together) increased exercise time by a mean of 53% compared to the 114% observed by Palange et al (2004) using a similar exercise protocol. Patients studied by Palange's group were more severely obstructed than those in the present study (FEV_1 38% vs 52% predicted, respectively), and may have been more limited by ventilatory constraints (Palange et al, 2004). Nevertheless, it is apparent that in my subjects, the increase in exercise tolerance with heliox was more associated with reduced dynamic hyperinflation than to increased V_E.

Important observations in the present study were the decreased perceptions of both dyspnea and leg fatigue at isotime with heliox. Although the primary outcome variables were physiologic in nature, the associated perceptual changes can result in the patients ceasing exercise (O'Donnell et al, 2001). The reduction in both dyspnea and leg fatigue symptoms at isotime with heliox may be important reasons for subjects continuing to exercise beyond isotime.

Limitations

There are three methodologic considerations that may influence the interpretation of these results. First, I recruited patients with moderate to severe COPD who were enrolled in a post-rehabilitation exercise program. Exercise-experienced patients were selected in order to minimize the effects of fear and anxiety that often limit exercise in patients who have not undergone exercise rehabilitation. It is possible that the results of this study may be altered in patients who are not exercise-experienced and who do not have moderate to severe disease were studied.

Second, as heliox has an effect on the flow resistance through the external tubing used to duct inspired and expired gas, others (Palange et al, 2004) matched the external resistance by added mesh screens to ensure that the effects of heliox were isolated to the airways. In contrast, I did not match the external resistance because our primary intent was to use heliox as a means to delay the ventilatory constraint and increase exercise tolerance.

Third, although MVICs and potentiated twitches may be the most recognized and most utilized methods of measuring fatigue (Gandevia 2001), they represent a static muscle contraction and may not be adequate in detecting the fatigue that occurs during dynamic muscle contractions. These methods, however, are currently considered the best methods for validity and reliability (Morton et al, 2005).

Clinical Implications

Heliox has been used previously during exercise training, but there is no added benefit to COPD patients compared to exercise training on room air (Johnson et al, 2002). However, my results suggest that it is only the patients who exhibit more ventilatory constraint and less leg muscle fatigue who will gain an exercise benefit from heliox. Therefore, when attempting to improve exercise tolerance in COPD, the relative importance of both leg muscle fatigue and ventilatory constraint should be considered.

4.5 CONCLUSIONS

I demonstrated that vastus lateralis contractile fatigue occurs in some COPD patients, which limits their ability to perform cycling exercise. In other patients without contractile fatigue, ventilatory constraint tends to be the cause for exercise intolerance. In this latter group, reducing ventilatory constraint with heliox increases exercise tolerance, which eventually causes greater contractile muscle fatigue.

Table 4-1. Subject demographics, baseline spirometry, and GXT results by whole sample and by fatiguers (F) and non-fatiguers (NF).

	F (n = 4)	NF (n = 7)	Total (n = 11)
Males/Females	3/1	3/4	6/5
Age (years)	63.0 ± 5.7	67.0 ± 8.2	65.5 ± 7.4
Height (cm)	169.8 ± 12.8	167.6 ± 10.9	168.4 ± 11.0
Weight (kg)	79.2 ± 24.3	78.3 ± 9.3	78.6 ± 15.2
FEV$_1$ (L)	2.0 ± 0.3	1.2 ± 0.5*	1.5 ± 0.6
FEV$_1$ (% pred)	66.0 ± 8.9	44.4 ± 15.3*	52.3 ± 16.8
FVC (L)	3.5 ± 0.3	3.3 ± 0.9	3.4 ± 0.8
FVC (% pred)	93.5 ± 29.0	84.4 ± 21.3	87.7 ± 20.6
FEV$_1$/FVC (%)	55.8 ± 4.2	37.2 ± 1.3*	44.0 ± 13.9
TLC (% pred)	120.8 ± 15.5	135.1 ± 11.3	129.9 ± 14.2
D$_L$CO (% pred)	81.5 ± 6.6	79.3 ± 17.3	80.1 ± 13.9
Room air MVIC (NM)	489.6 ± 293.3	344.3 ± 103.2*	397.1 ± 193.8
VO$_{2peak}$ (ml·kg^{-1}·min^{-1})	17.1 ± 5.3	12.6 ± 3.5	14.2 ± 4.6
WR$_{peak}$ (W)	92.5 ± 33.0	74.3 ± 25.1	80.9 ± 28.1
V$_{Epeak}$ (L·min^{-1})	58.2 ± 17.9	38.2 ± 11.7*	45.5 ±16.8
V$_E$/MVV (%)	83.3 ± 18.1	95.6 ± 17.6*	91.2 ± 17.9
SpO$_2$ (%)	93.5 ± 1.7	87.0 ± 4.9*	89.4 ± 5.1
Reason for stopping			
Dyspnea (n)	1	3	4
Leg fatigue (n)	3	2	5
Both equally (n)	0	2	2

Data presented as mean ± SD. *$p<0.05$ vs F. FEV$_1$ = forced expiratory volume in one second, FVC = forced vital capacity, TLC = total lung capacity, D$_L$CO = diffusion capacity of the lung for carbon monoxide, MVIC = maximal voluntary isometric contraction, VO$_{2peak}$ = peak oxygen consumption, WR$_{peak}$ = peak work rate, V$_{Epeak}$ = peak minute ventilation, SpO$_2$ = oxygen saturation

Table 4-2. Resting pulmonary function data for all subjects (n=11) breathing air (RA) or heliox (HE).

	RA	HE
FEV_1 (L)	1.41 ± 0.58	1.58 ± 0.68*
FVC (L)	2.87 ± 0.87	2.96 ± 0.95
FEV_1/FVC (%)	47.8 ± 8.1	52.0 ± 10.97*
PEF ($L \cdot s^{-1}$)	6.40 ± 2.64	7.94 ± 3.38*
V_E ($L \cdot min^{-1}$)	14.8 ± 5.25	13.88 ± 5.44
V_T (L)	0.90 ± 0.38	0.79 ± 0.36
RR (breaths/min)	17.2 ± 3.7	18.1 ± 3.6
EELV (% TLC)	65.8 ± 8.2	63.3 ± 7.9
EILV (%TLC)	78.4 ± 7.3	74.3 ± 7.2

Data presented as mean ± SD. *$p<0.05$. FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, PEF = peak expiratory flow rate, V_E = minute ventilation, V_T = tidal volume, RR = respiratory rate, EELV = end-expiratory lung volume, EILV = end-inspiratory lung volume, TLC = total lung capacity.

Table 4-3. Selected end exercise results from the constant load exercise trials for all subjects (n=11) breathing air (RA), heliox at symptom limitation (HE), or heliox at isotime (ISO).

	RA	ISO	HE
Tolerance time (s)	355 ± 158	N/A	530 ± 270*
SpO_2 (%)	88.7 ± 5.0	92.1 ± 3.0*	90.9 ± 3.9
HR (beats per minute)	128.0 ± 14.7	125.5 ± 17.3	131.2 ± 18.5
RR (breaths per minute)	33.9 ± 6.7	31.7 ± 7.1	35.4 ± 9.8
V_T (L)	1.35 ± 0.44	1.48 ± 0.52	1.42 ± 0.48
V_E ($L \cdot min^{-1}$)	45.6 ± 15.1	45.9 ± 16.2	50.3 ± 19.8
V_T/IC (%)	80.9 ± 10.7	73.5 ± 10.2*	79.3 ± 12.7
V_E/MVV (%)	96.3 ± 20.0	88.3 ± 14.4	94.5 ± 22.0
5min MVIC (% baseline)	99.0 ± 18.5	99.6 ± 12.0	90.8 ± 10.3*†
5min TwVL (% baseline)	85.7 ± 11.0	84.1 ± 11.0	72.4 ± 7.0*†
5min VA (% baseline)	103.8 ± 11.2	101.7 ± 5.6	99.9 ± 6.9
Dyspnea (/10)	5.5 ± 2.6	3.3 ± 2.0*	5.8 ± 2.9†
Leg Fatigue (/10)	5.2 ± 2.7	3.6 ± 1.7*	5.9 ± 2.7†
Reason for stopping			
Dyspnea (n)	6	N/A	4
Leg fatigue (n)	5	N/A	5
Both equally (n)	0	N/A	2

Data presented as mean ± SD. *$p<0.05$ vs RA, †$p<0.05$ vs ISO. SpO_2 = oxygen saturation, HR = heart rate, RR = respiratory rate, V_T = tidal volume, V_E = minute ventilation, IC = inspiratory capacity, MVV = maximal voluntary ventilation, MVIC = maximal voluntary isometric contraction, TwVL = vastus lateralis twitch torque, VA = voluntary activation.

TABLE 4-4. Selected end exercise data from the constant load trials for fatiguers (F) and non-fatiguers (NF) breathing air (RA), heliox at symptom limitation (HE), or heliox at isotime (ISO).

	RA		HE		ISO
	F	NF	F	NF	NF
Exercise time (s)	355 ± 32	355 ± 203	391 ± 82	610 ± 317*†	N/A
RR (breaths/min)	34.7 ± 8.0	33.5 ± 6.38	37.8 ± 13.0	34.1 ± 8.4	30.3 ± 6.85
V_T (L)	1.65 ± 0.47	1.18 ± 0.34†	1.70 ± 0.46	1.29 ± 0.44†	1.34 ± 0.50‡
V_E ($L \cdot min^{-1}$)	56.2 ± 14.0	39.6 ± 12.8†	56.0 ± 15.8	48.3 ± 16.5†	39.5 ± 14.0
VO_2 ($L \cdot min^{-1}$)	1.45 ± 0.38	1.14 ± 0.26†	1.43 ± 0.35	1.21 ± 0.36†	1.09 ± 0.37
VCO_2 ($L \cdot min^{-1}$)	1.43 ± 0.31	1.06 ± 0.33†	1.49 ± 0.37	1.09 ± 0.36†	1.03 ± 0.37
VT/IC (%)	77.0 ± 13.4	83.2 ± 9.3	70.8 ± 15.1	84.2 ± 8.8†	74.4 ±12.0‡
V_E/MVV (%)	83.3 ± 17.8	103.8 ± 18.1†	70.8 ± 12.0*	103.2 ± 17.6†	94.6 ± 10.3‡
Dyspnea (/10)	4.5 ± 3.9	6.0 ± 1.7†	5.4 ± 3.6	6.0 ± 2.7	3.6 ± 1.7‡
Leg Fatigue (/10)	3.5 ± 1.7	6.1 ± 2.7†	3.5 ± 1.3	7.3 ± 2.2†	3.7 ± 1.9‡
Reason for stopping					
Dyspnea (n)	3	3	3	1	NA
Leg fatigue (n)	1	4	1	4	NA
Both equally (n)	0	0	0	2	NA

Data presented as mean ± SD. *$p<0.05$ vs corresponding RA value, †$p<0.05$ vs F within each test condition, ‡$p<0.05$ vs NF RA. RR = respiratory rate, V_T = tidal volume, V_E = minute ventilation, VO_2 = oxygen consumption, VCO_2 = carbon dioxide production, IC = inspiratory capacity, MVV = maximal voluntary ventilation.

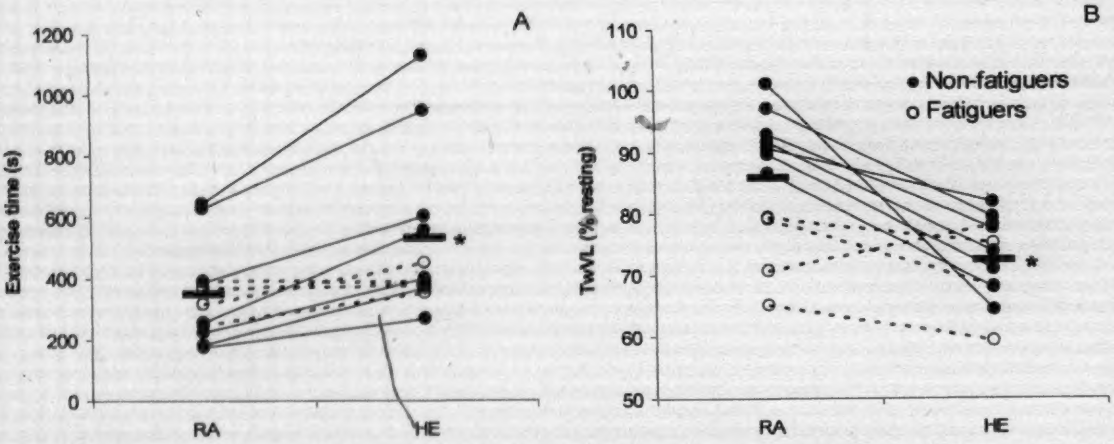

FIGURE 4-1. Individual data for exercise time (A) and 5 minute vastus lateralis twitch torque (B) for the room air (RA) and heliox (HE) tests. Subject data points are separated into fatiguers (open circles, dashed lines) and non-fatiguers (closed circles, solid lines). The horizontal bars indicate mean values. $*p<0.05$ vs RA mean.

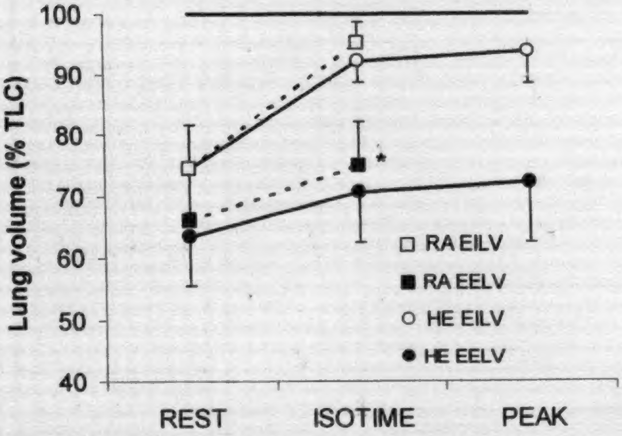

FIGURE 4-2. Exercise lung volumes for all subjects during the room air (RA) and heliox (HE) trials at peak exercise and isotime. EILV = end-inspiratory lung volume, EELV = end-expiratory lung volume. *p<0.05 vs HE at isotime.

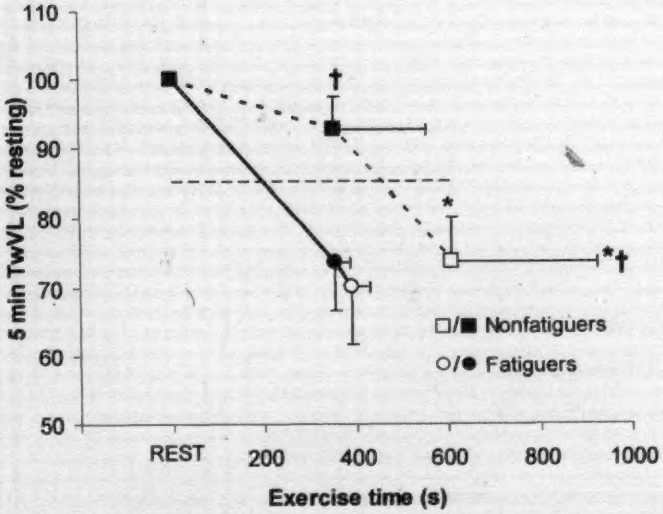

FIGURE 4-3. 5 minute TwVL scores related to exercise time. RA (closed) and HE (open) for fatiguers (circles) and non-fatiguers (squares). *p<0.05 vs RA, †p<0.05 vs fatiguers.

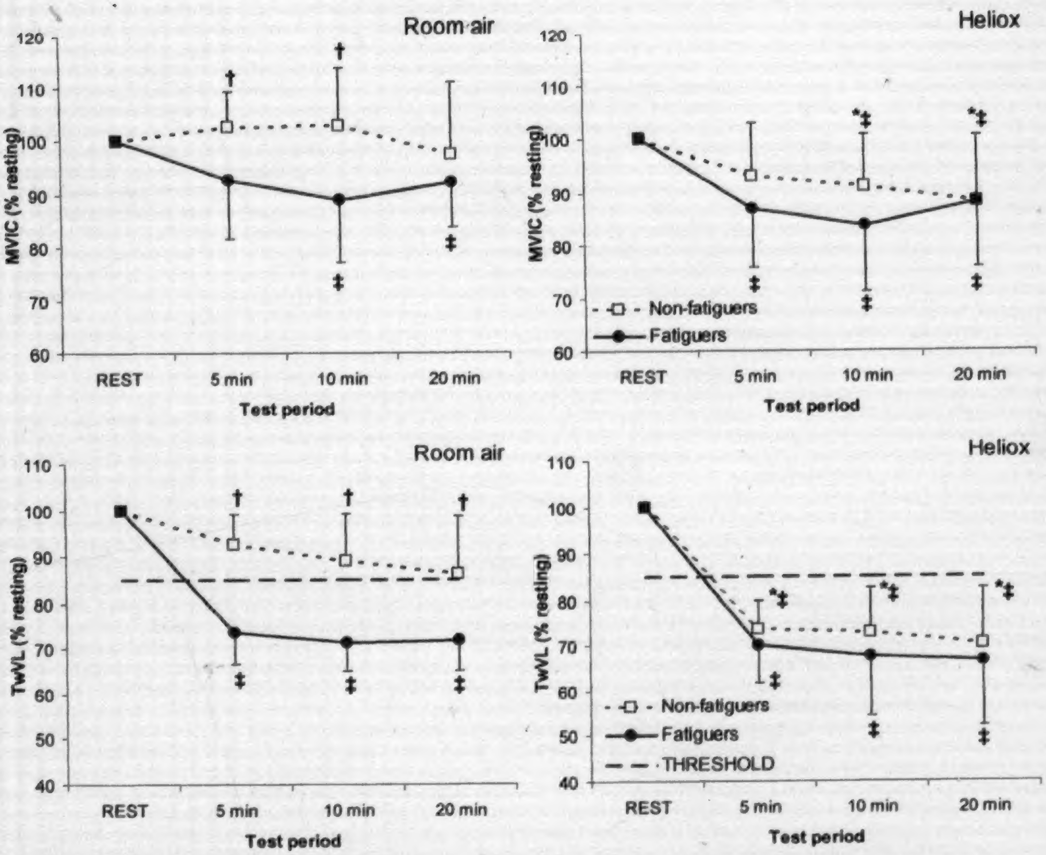

FIGURE 4-4. Voluntary quadriceps muscle torque (top) and vastus lateralis twitch torque (bottom) after room air (left) and heliox (right) tests for both fatiguers and non-fatiguers. For the TwVL measurements, the horizontal dotted line represents the 85% fatigue threshold. *$p<0.05$ vs corresponding value on room air test, †$p<0.05$ vs fatiguers, ‡$p<0.05$ vs pre-test resting value.

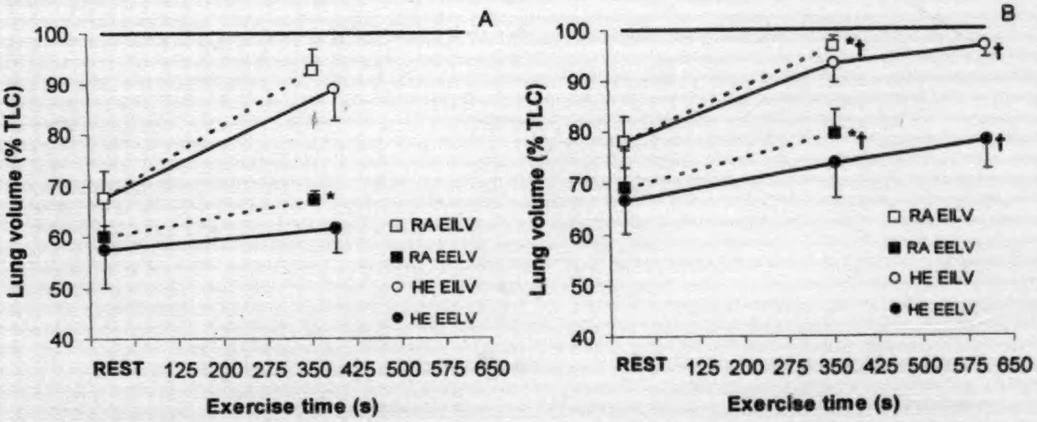

FIGURE 4-5. Exercise lung volumes in fatiguers and non-fatiguers. Resting and peak exercise volumes in fatiguers (A) and resting, isotime, and peak exercise volumes in non-fatiguers (B). EILV = end-inspiratory lung volume, EELV = end-expiratory lung volume.*$p<0.05$ vs RA, †$p<0.05$ vs corresponding peak exercise value in fatiguers.

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CHAPTER FIVE
GENERAL DISCUSSION

5.1 SUMMARY AND ANALYSIS OF WORK COMPLETED

The general aim of the research conducted for this thesis was to examine the nature and impact of modifications to ventilatory capacity in populations who exhibit ventilatory limitation during exercise. Specifically, the first study examined the hypotheses that the self-contained breathing apparatus (SCBA) regulator, which imposes a significant expiratory resistance at high ventilation rates, would increase work of breathing (WOB) (partially due to expiratory resistive work) and would impose a ventilatory constraint during cycle ergometery exercise. The second study hypothesized that the SCBA would increase WOB, increase the constraint on ventilation, increase respiratory muscle fatigue, and reduce maximal expiratory flow rate during repeated stair stepping exercise and that breathing heliox would, at least partially, reduce these effects. The third and final thesis study hypothesized that delaying the ventilatory constraint to cycling exercise in patients with chronic obstructive pulmonary disease (COPD) by breathing heliox would increase exercise tolerance and leg muscle fatigue, and that the effect of heliox would be greatest in those patients who were more limited initially by ventilatory constraint, rather than leg fatigue.

The first study, presented in Chapter Two, used submaximal cycling exercise inside a custom-built body plethysmograph (body box) to measure the WOB and exercise lung volumes imposed by the SCBA regulator compared to a low resistance breathing valve. Esophageal pressure was used to estimate the change in pleural pressure and it was plotted against lung volume changes to create modified Campbell diagrams. Campbell diagrams can be used to specifically calculate the resistive and elastic WOB during both inspiration and expiration. Although this technique has been used by others either in response to voluntary hyperinflation (Jennings et al, 1987) or in patients with COPD who dynamic hyperinflate during exercise (Eves et al, 2006; Sliwinski et al, 1998), I believe this is the first study that has examined WOB in this manner during exercise in healthy subjects. The elements that were unique to the methodology used in this study were: (a) the determination of the expiratory resistive and elastic components of WOB that are due to the reductions in end-expiratory lung volume (EELV) below functional residual capacity; (b) the use of a dynamically measured lung compliance curve rather than a straight line estimated from the zero flow points during each breath; and (c) the use of body plethysmography to determine change in lung volumes.

The key findings of this first study were: (a) compared to the low resistance breathing valve the SCBA regulator significantly increased total WOB when minute ventilation reached 85 L/min and WOB increased by 13% when ventilation rate reached 112 L/min; (b) the net increase in total WOB was due to the combination of increased inspiratory elastic (by 32%) and expiratory resistive (by 59%) WOB at the highest work rate; and (c) the resistance of the regulator caused subjects to breathe at higher lung volumes compared to the low resistance breathing valve, which resulted in a 13% decrease in inspiratory capacity at the highest work rate.

One of the more interesting findings of this first study was that despite the fact that the SCBA regulator increases *expiratory* resistance, which explained much of the decreased ventilation observed by Eves et al (2005) during maximal exercise, it was the *inspiratory* WOB that contributed most of the increase in total WOB. This finding supports research in healthy subjects that demonstrated that breathing with an increased expiratory resistance increases lung volumes in some circumstances (Iandelli et al, 2002) and the increase in lung volumes increases the elastic work of inspiration for a given tidal volume (Roussos and Campbell, 1986). The increased lung volumes with the SCBA regulator resulted in a plateau in end-inspiratory lung volume (EILV) at approximately 90% of vital capacity as early as the 180 Watt stage. This EILV translates to an absolute inspiratory reserve volume (IRV) of 0.58L, which approaches the "minimal IRV" defined by O'Donnell et al (2001) in patients with COPD. The above findings together suggest that the ventilatory limitation observed by Eves et al (2005) with the SCBA may be partly due to a constraint on tidal volume expansion and partly due to increased total WOB. In order to confirm this suggestion, work of breathing and exercise lung volumes should be measured during maximal exercise to exhaustion.

The cause of the increased lung volumes with the SCBA regulator is unknown; however, there are two plausible mechanisms. First, the presence of an expiratory flow limitation (EFL) has been shown to increase lung volumes during exercise (Iandelli et al, 2002; McClaran et al, 1999). An EFL with the SCBA has not been demonstrated; however, Eves et al (2005) found that expiratory flow rate at peak exercise was decreased suggesting an EFL was possible. In the first thesis study, Figure 2-6 shows similar findings during the final work rate, providing indirect evidence supporting this contention. Direct measurement of an EFL with the SCBA has not been reported. Second, if an EFL is not present, the increased expiratory resistance with the SCBA regulator may cause the increased lung volumes. In Chapter Two, I speculated that the increased pressure required to overcome the greater expiratory resistance with the SCBA regulator may cause an unaccustomed level of expiratory muscle WOB for a given level of ventilation. It is possible that the normal decrease in EELV would be less than with the low resistance breathing valve in order to decrease the expiratory elastic WOB and minimize the rise in total expiratory WOB. In support of this suggestion, McClaran et al (1999) demonstrated that lung volumes with expiratory loading increased prior to the development of an EFL, which indicates that it was the increased resistance to expiration that caused the shift in lung volumes. Even if expiratory flow was not limited by the maximal flow-volume envelope, the increased resistance for a given level of expiratory pressure generation may cause a reduction in expiratory flow and may also explain the findings of attenuated expiratory flow at higher ventilation rates. The consequence of the higher lung volumes, however, is a disproportionate rise in inspiratory elastic WOB, which contributes the bulk of the increase in total WOB. Further study is required to determine the mechanisms for the increased lung volumes during exercise.

It must be emphasized that the results of Study One apply to exercise on a cycle ergometer with subjects wearing t-shirts and shorts and only the SCBA regulator. Certainly, wearing full firefighting gear including the full SCBA (including the compressed air tank and harness) and performing an exercise mode that more closely approximates firefighting work could alter the ventilatory response to heavy exercise. Therefore, Study Two (presented in Chapter Three) was designed to assess the reduction in ventilatory capacity imposed by the SCBA regulator while subjects wore firefighting equipment and performed stepping exercise. Additionally, because heliox has been shown to improve exercise tolerance and maximal ventilation in subjects wearing an SCBA (Eves et al, 2003a), and because heliox has an effect on reducing ventilatory constraint (see Chapter One, section 1.2.3), this gas mixture was used to examine the impact of reducing ventilatory limitations on ventilatory mechanics with the SCBA. Finally, the effect of the SCBA regulator on resting pulmonary function was examined in order to provide further evidence related to the contention that an EFL may occur with the SCBA.

This second study used the same body box as was used in the first study, but an extra 33 cm of height was added by cutting a hole in the roof of the box and adding a Plexiglas extension. The additional height allowed taller subjects to perform stepping exercise inside the box. Respiratory muscle fatigue was determined by the measurement of pre and post exercise maximal inspiratory and expiratory pressures. WOB and exercise lung volumes were determined in a similar fashion to the first study, however, because the firefighting jacket and SCBA harness and cylinder impose a load on the chest wall, using predictions of chest wall compliance to create Campbell diagrams could have been inaccurate. Therefore, in firefighting jacket and SCBA harness, the chest wall compliance needed to be measured in order to obtain a more accurate representation of the chest wall contribution to elastic and resistive WOB. Accurate measurement of chest wall compliance requires considerable practice to ensure full respiratory muscle relaxation (Estenne et al, 1985). Although the baseline compliance, measured in each subject in t-shirt and shorts, was very similar to that reported previously (Estenne et al, 1985), it was impossible to know if each subject achieved true 'full' relaxation. Nevertheless, because the chest wall compliance curve with the harness was used to create a more accurate representation of compliance than the method used in the first study, it merely served as a marker to separate the four components of WOB for each of the three experimental conditions. The same curve was used in the analysis of all three conditions, and therefore, any error in measurement of chest wall compliance would be consistent across conditions and would not affect the WOB results.

The key findings of this second study were: (a) total WOB was increased after 30 minutes of stepping exercise with the SCBA regulator and compressed air (BA-A) by 58% compared with the low resistance breathing valve (RV), which was due to increases in inspiratory (by 55%) and expiratory (by 133%) WOB, (b) exercise lung volumes were elevated with the BA-A such that EELV was 12% higher and EILV was 7% higher than the RV, (c) the BA-A caused a significant level of both inspiratory and expiratory muscle fatigue, (d) at rest, pulmonary function was significantly impaired with the BA-A, and (e) breathing heliox (BA-H) with the SCBA reduced the above effects to remarkably similar levels as the RV except for a more pronounced effect on resting pulmonary function measures (FEV$_1$, peak expiratory flow, and maximal mid-range expiratory flow rate). The effect of heliox in reducing exercise lung volumes and reducing flow resistance is evidenced by the reduced levels of both inspiratory muscle fatigue and expiratory muscle fatigue, respectively, compared with the SCBA and compressed air.

This second study provided additional information related to the impact of the SCBA on ventilatory function. The addition of the SCBA tank and harness, fire protective gear, and repeated stepping exercise in this study compared with the first, altered ventilatory mechanics and the relative contributions to total work of breathing in several significant ways. As mentioned in Chapter Three, the SCBA harness and cylinder reduced the chest wall compliance, resulting in: a) a reduction in functional residual capacity, b) a lowered expansion of tidal volume via increases in EILV, and c) an increase in the inspiratory elastic work required to increase tidal volume. Despite a slightly lower ventilation rate, the markedly lower peak tidal volume obtained in Study Two, compared with the final work rate in Study One, caused inspiratory elastic work with the SCBA regulator to be considerably greater in Study Two (2057 vs. 1385 $cmH_2O{\cdot}L{\cdot}min^{-1}$), which reflects the relative changes in chest wall compliance. The lower resting EELV and the changes in chest wall recoil, however, were in favour of a reduced total expiratory WOB compared with Study One (425 vs. 957 $cmH_2O{\cdot}L{\cdot}min^{-1}$) due to reductions in both the expiratory elastic and resistive components. Despite the lowered total expiratory WOB, significant levels of expiratory muscle fatigue were present after exercise with the SCBA regulator and may have an impact on work performance.

Another interesting effect of the change in conditions for Study Two was an alteration in exercising lung volume response. In Study One, a plateau in both EELV and EILV was observed at lower levels of exercise intensity. The plateau in EELV could have been due to either a mechanical flow limitation or, more likely, to the increased expiratory pressure generated by the SCBA regulator. In Study Two, however, although EELV was higher in the BA-A, it increased slightly across each exercise bout in all three conditions. Although maximal peak expiratory flow rates were reduced with the SCBA, maximal mid expiratory flow rates were preserved. At the range of lung volumes used during exercise (Johnson et al. 1999), there was no evidence that reduced maximal flow rates occurred (Figure 3-5), indicating that a mechanical limitation to exercising airflow is unlikely. This suggestion is supported by the fact that heliox increased maximal mid expiratory flow rates to a greater level than either the RV or the BA-A (Figure 3-5), but there was no increase in exercise expiratory flow rates (Table 3-2). Together these findings strongly suggest that the presence of an EFL is unlikely and would not be the cause of the increased lung volumes. In order to test this hypothesis, however, some measure of expiratory flow limitation would be required (such as plotting exercise flow-volume loops within maximal loops; Johnson et al, 1999). Although exercise flow and volume were measured in Study Two, it would be difficult to determine if a flow limitation occurred if body box measured flow-volume curves were placed within spirometer measured maximal flow-volume curves because of the difference observed in maximal mid expiratory flow rates between the two methods due to the effects of gas compression on spirometric-measured expiratory flow (Coates et al. 1988).

In addition, in Study One, EILV plateaued at approximately 90% of forced vital capacity (FVC) when ventilation reached 70 L·min^{-1} and appeared to constrain any further increase in tidal volume. Whereas in Study Two, EILV was lower (83%) at approximately 75 L·min^{-1} and continued to climb to 87% of FVC at the end of thirty minutes of exercise, indicating that the mechanical constraint on tidal volume was not evident, at least in the early stages of exercise. It is possible, however, further increases in EILV, and hence tidal volume, would have been intolerable due to the greater level of inspiratory WOB observed in the present study. It is possible, in fact, that the constraining effect of the SCBA harness on lung volume expansion prevents an even further rise in inspiratory WOB. In order to address these speculations, further study involving maximal exercise and examination of these differences imposed by the harness would need to be performed.

Studies One and Two provide evidence that the increased expiratory resistance with the SCBA regulator causes higher exercise lung volumes, increased levels of respiratory muscle work, and the potential for a constraint on tidal volume expansion. This reduction in ventilatory capacity at least partially explains the limitation on ventilation during maximal exercise observed by Eves et al (2005) and may be expected to occur during heavy fire fighting task of similar ventilation rates (Holmer and Gavhed, 2007). As discussed in Chapter Two, however, there are several potential cardiovascular and skeletal muscle consequences of these ventilatory changes including reductions in stroke volume and cardiac output (Stark-Leyva et al, 2004; Harms et al, 1998) due to the increased intrathoracic pressure swings and EFL (Miller et al, 2006), redistribution of skeletal muscle blood flow (Harms et al, 1997), and the development of early and/or increased skeletal muscle fatigue (Romer et al, 2006). In Studies One and Two, these consequences were not measured; however, the presence of any of them would have a significant impact on exercise and work ability. As well, because heliox can reverse the ventilatory changes associated with the SCBA, improvement in the cardiovascular and muscular consequences could be expected. Future studies in this area should examine these factors with the SCBA as well as their impact on work performance.

One population where there is an emerging body of evidence on the impact of ventilatory and peripheral constraints during exercise in patients with COPD. As mentioned in Chapters One and Four, patients with COPD exhibit both ventilatory and skeletal muscle limitations at symptom-limited exercise, but there is no consensus regarding how those limitations interact. The results of the first two thesis studies and the work of others (Romer et al, 2006; Palange et al, 2004; Saey et al, 2003; O'Donnell et al, 2001) led to Study Three, presented in Chapter Four, which examined the interaction between ventilatory limitation and leg muscle fatigue in COPD patients. Although subjects wearing an SCBA and patients with COPD both show increases in expiratory resistance and reductions in expiratory flow rates, the mechanisms behind these changes and the potential effects of heliox are very different. The site of increased expiratory resistance with the SCBA is the regulator itself, a resistance external to the airways, where there would likely be a greater susceptibility to turbulent airflow with exercise. The chief site of airflow resistance in patients with COPD is in the smaller airways (Gelb et al, 1981) and the reductions in lung elasticity and airway tethering accompanying the disease usually exacerbate the flow resistance during expiration through airway compression. Consequently, EFL is a chief concern for these patients (Gelb et al, 1981). Thus, with an increased expiratory resistance, increased expiratory pressure to overcome this resistance would result in increased airflow rates in the SCBA, but decreased airflow rates in COPD patients. In addition, heliox would likely have a greater effect on reductions in resistive WOB for a given level of ventilation in the SCBA due to the increased susceptibility to changes in airflow resistance with turbulent airflow. In contrast, airflow resistance, and therefore WOB, would change to a lesser degree with heliox in patients with COPD (as demonstrated by Eves et al 2006); however, the increase in maximal expiratory flow with heliox in patients with COPD would have a larger effect on EFL, and therefore, lung volumes (Palange et al 2004). Despite the differences in mechanisms of the abnormal ventilatory mechanics, a strikingly similar effect on ventilatory capacity was observed. In both populations, the increased flow resistance and reduced expiratory flow rates cause greater lung volumes, increased potential for ventilatory constraint, and increased inspiratory and expiratory WOB (Chapter Two; Chapter Three; Yan et al, 1997). Similarly, the effect of heliox in reducing the ventilatory constraint (Chapter Three and Palange et al, 2004) and increasing exercise tolerance (Eves et al, 2003a; 2006) is consistent in both populations. Therefore, some of the basic underlying questions generated from the results of Studies One and Two were applied to patients with COPD in Study Three.

Study Three used constant load cycling exercise to symptom-limitation to examine the degree of ventilatory constraint and leg muscle fatigue in patients with COPD. Subjects breathed either room air or heliox. Additionally, subjects breathed heliox for a third trial that was stopped by the investigators at isotime to examine the effect of acute unloading on leg fatigue at the point of equal work performed. Inspiratory capacity and exercise lung volumes were measured periodically during exercise and at symptom-limitation with a dry rolling spirometer and bag-in-box system. Prior to and after exercise, maximal voluntary isometric contractions were performed with and without magnetic motor point stimulation. Additionally, resting potentiated twitches were measured before and after exercise. Subjects were classified as fatiguers or non-fatiguers based on the degree of fatigue in the potentiated twitches after the room air trial. Results from subjects were analyzed as a whole group and also between groups.

Magnetic stimulation of the femoral nerve has been used extensively in this patient population as a means of measuring non-volitional muscle strength and fatigue of the quadriceps muscles (Mador et al, 2003). Although it is considered painless relative to electrical stimulation (Man et al, 2004), there is still a large degree of discomfort associated with repeated stimulations over the femoral triangle. As such, direct vastus lateralis motor point magnetic stimulation was chosen as a more comfortable alternative. Direct stimulation of the quadriceps motor point has been used in patients with COPD as an indicator of muscle activity and is considered superior to nerve stimulation by some (Gosselin et al, 2003). As well, direct motor point stimulation has been used to produce both interpolated and potentiated twitch measurements (Morton et al, 2005; Todd et al, 2004) and has excellent reproducibility and low variability (Todd et al, 2004). In producing potentiated and interpolated twitches, the stimulation magnitude must high enough to produce a maximal motor unit action potential (M-wave) (Man et al, 2004; Shield and Zhou, 2004). The technique used in Study Three produced clear, maximal M-waves in all subjects at a mean of 83% of maximal stimulator intensity. As all tests were performed at 100% stimulator intensity, supramaximal intensity was ensured. All patients tolerated the procedures well with minimal discomfort. For more details regarding this technique, please refer to Appendix A.

The key findings of this third study were: (a) heliox breathing delayed the ventilatory constraint observed with room air breathing and it increased exercise tolerance by 53% in the whole subject sample, (b) the increased exercise tolerance in the whole sample was associated with a 16% increase in vastus lateralis contractile fatigue, (c) when subjects were classified into fatiguers and non-fatiguers, the non-fatiguers demonstrated greater levels of ventilatory constraint at symptom limitation on the room air test (EILV = 97% of TLC; peak exercise minute ventilation / maximal voluntary ventilation = 104%), (d) the non-fatiguers also increased exercise tolerance (by 77%) with heliox which resulted in a 21% increase in leg muscle fatigue; whereas the fatiguers did not increase exercise tolerance, nor the level of leg fatigue despite an improvement in ventilatory constraint, (e) there was a significant negative correlation between the degree of ventilatory constraint and the degree of leg muscle fatigue across all subjects (r = -0.77), and (f) at isotime with heliox there was no difference in the degree of leg muscle fatigue in either the fatiguers or non-fatiguers compared with the room air test.

The response to delaying the ventilatory constraint during exercise depends on the nature of the initial exercise limitation. It appears that those who were limited by ventilatory constraint on the room air test were unable to exercise long enough to adequately fatigue their leg muscles. Once the ventilatory constraint was relieved, exercise tolerance, and consequently, the level of leg muscle fatigue were increased. Those patients who were more limited by leg fatigue did not respond to the relief of the ventilatory constraint by increasing exercise tolerance or leg fatigue. These results support the crucial study by Saey et al (2003) who demonstrated similar findings related to the effect of ipratropium bromide on leg muscle fatigue. In that study, however, the degree of ventilatory constraint was not measured. Study Three of this thesis provides new evidence that indicates that, in a relatively heterogeneous and exercise-experienced group of patients with COPD, the degree of ventilatory limitation observed during room air exercise is inversely related to the degree of leg muscle fatigue.

The intent of Study Three was not to examine all of the potential effects of heliox on the improvements in ventilatory capacity and the subsequent changes in muscle fatigue; however, some inferences can be made based upon the data. As mentioned in Chapter One, limitations on ventilatory capacity may be due to increases in ventilatory constraint or increases in the WOB. The results of Study Three and the findings of others (Palange et al, 2004) demonstrate clearly that heliox breathing reduces exercise lung volumes and the ventilatory constraint associated with ventilatory limitations in patients with COPD. What is not known is the effect of heliox breathing on the WOB and the potential alterations in muscle blood flow (Harms et al, 1997). As discussed in Chapter One, patients with COPD have an increased WOB for a given work rate compared to healthy matched controls (Mador et al, 2003) that may cause reflex reductions in leg oxygen delivery and partially contribute to the development of leg muscle fatigue (Romer et al, 2006). It has been suggested that a reduction in WOB should decrease the level of leg muscle fatigue observed by increasing the leg muscle blood flow in healthy athletes exercising at very high intensities (Romer et al, 2006). In Study Three, WOB was not measured and the subjects exercised at much lower absolute intensities than the subjects studied by Romer and colleagues. Therefore, it is inappropriate to generalize the findings of Romer et al (2006) to the patients with COPD in Study Three. Although it is possible that WOB was decreased, it did not significantly delay the onset of leg muscle fatigue. Eves et al (2006), however, found that normoxic heliox did not decrease total WOB at isotime, which supports the contention that the effect of heliox on ventilatory capacity was not due to alterations in respiratory muscle load. Therefore, the main effect of heliox in these patients was to reduce the level of dynamic hyperinflation and ventilatory constraint.

An interesting finding, discussed in Chapter Four, was the response of the one patient who was classified as a fatiguer, but also increased exercise tolerance (by 43%) and leg muscle fatigue (by 14%) with heliox breathing. This patient also demonstrated significant signs of attaining a limitation on ventilatory capacity (tidal volume / inspiratory capacity = 95% and EILV = 98% of TLC), indicating that he was most likely more limited by ventilatory constraints than by leg fatigue. This finding reinforces the importance of understanding that muscle fatigue does not necessarily imply imminent exercise cessation (Hunter et al, 2004) and that a standardized, defined degree of muscle fatigue is likely inadequate in predicting exercise limitation or the response to heliox breathing in every patient.

These findings have important implications for exercise rehabilitation of patients with COPD. Although it may be impractical to perform detailed physiologic testing on every patient admitted into pulmonary rehabilitation programs, the information gained from this testing can provide the most appropriate direction for the management of that patient. In a rehabilitation setting, other measurements of leg strength and fatigue, such as maximal voluntary isometric contractions (MVIC), may be useful in lieu of the use of muscle twitch torque to separate patients into fatiguers and non-fatiguers. Although MVICs were not as sensitive as potentiated twitches to the detection of fatigue (see Figure 4-4), they may provide a reasonable estimate to help guide rehabilitation exercise prescription. For example, a patient that falls into the non-fatiguer category (hence, more ventilatory limited) would likely benefit from measures that reduce the ventilatory demand or the ventilatory constraint during exercise, such as supplemental oxygen (O'Donnell et al, 2001), bronchodilators (Saey et al, 2003), heliox (Palange et al, 2004), interval exercise (Vogiatzis et al, 2004), and small muscle mass exercise (Richardson et al, 1999). Patients who fall more into the fatiguer category will benefit less from these measures and standard exercise rehabilitation program may be sufficient. The results of this study do not provide direct evidence that training outcomes will be enhanced with heliox in the non-fatiguers; however, it stands to reason that the potential training response should be greater if exercise is of longer duration and if the leg muscles can be utilized to a greater degree, and heliox breathing does this.

5.2 CONCLUSIONS

Evidence of a limitation on ventilatory capacity has been documented in healthy subjects breathing from an SCBA during both cycling and stepping exercise. The increased expiratory resistance caused elevated EELV, a greater level of WOB, and increased respiratory muscle fatigue than the low resistance breathing valve. Breathing a normoxic helium gas reduced the level of ventilatory constraint and the WOB with the SCBA and ameliorated the level of respiratory muscle fatigue. In patients with COPD, a similar constraint on ventilation was observed, and has been reported previously, which directly contributed to exercise limitation in some patients. Heliox breathing increased exercise tolerance and leg muscle fatigue after symptom-limited exercise only in those patients who were more ventilatory limited than leg limited. In conclusion, reducing flow resistance with heliox breathing significantly affects the degree of ventilatory constraint, work of breathing, and respiratory muscle fatigue in subjects wearing an SCBA, and also increases exercise tolerance, delays dynamic hyperinflation, and promotes greater peripheral muscle fatigue in patients with COPD.

5.3 RECOMMENDATIONS FOR FUTURE RESEARCH

Based upon the findings of this thesis research, there are several recommendations for future work in this area. Firstly, as the studies performed in Chapters Two and Three provide some initial evidence that limitations on ventilatory capacity with the SCBA may be responsible for the reductions in maximal exercise ventilation and performance, future studies should explore this hypothesis further and attempt to determine some of the consequences of the ventilatory limitations that may impact a firefighter's work performance and/or health. Specifically, the hypothesis that the ventilatory changes observed with the SCBA play a role in reducing maximal exercise ventilation and exercise tolerance should be tested. As Studies One and Two did not specifically take subjects to maximum, the assumption that the changes observed will influence maximal exercise needs to be investigated, although the levels of exercise in my studies may better represent the occupational reality (Holmer and Gavhed, 2007).

Secondly, utilization of heliox breathing reduces the ventilatory constraints with the SCBA and, similar to the findings in Chapter Four with patients with COPD, the systemic consequences of alterations in respiratory muscle load should be examined. The large intrathoracic pressure swings, the increased WOB, and the presence of respiratory muscle fatigue with the SCBA may cause alterations in cardiovascular function (Miller et al, 2006) or exercising muscle function (Romer et al, 2006). These alterations may have an impact on occupational performance, but may also be contributing factors in the development of heart disease in firefighters (Choi, 2000). Therefore, examining the effects of heavy work with the SCBA on heart function would be important.

Thirdly, the findings of Chapter Four indicate that the response to acute exercise in patients with COPD is somewhat different depending on the nature of the limitation to exercise. This finding suggests that exercise rehabilitation programs that are able to determine an individual patient's primary source of exercise limitation would be able to better design exercise training to fit the patient's ability to respond. Certainly, patients with less ventilatory limitation during exercise would likely benefit physiologically more from whole body aerobic training (standard rehabilitation) than those with more ventilatory limitation (Plankeel 2005); whereas patients with ventilatory limitation may benefit more from methods that reduce ventilatory constraint during exercise, such as interval training and heliox breathing during training. Interval training is also a promising method in pulmonary rehabilitation as it has been shown to induce significant peripheral muscle benefit with fewer symptoms (Vogiatzis et al, 2005) and less ventilatory constraint (Vogiatzis et al, 2004) than continuous exercise.

Fourthly, the use of heliox during rehabilitation has not been demonstrated to be superior to air breathing during rehabilitation (Johnson et al, 2002), but perhaps stratification of patients into training subgroups (as above) might improve outcomes. Future studies should compare other methods of reducing ventilatory constraint in the ventilatory limited patients with the response in leg muscle limited patients both during acute exercise and after rehabilitation.

Fifthly, the findings of this thesis research should be applied to other populations that are known to exhibit potential ventilatory limitation during exercise such as healthy older subjects (Johnson et al, 1991), healthy females (McClaran et al, 1998), and in elite endurance athletes (Johnson et al, 1992). The techniques used to measure and alter ventilatory constraint, WOB, and leg muscle fatigue could be used in these populations to determine the impact of ventilatory limitations on exercise performance and exercise training.

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Appendix A
ADDITIONAL METHODOLOGY

A.1 Body Plethysmography

In Chapters Two and Three, a custom-built body plethysmograph (body box or box) was used to measure lung volume changes during exercise. The purpose of this section is to outline some of the steps required and the selected relevant issues surrounding the design, construction, validation, and usage of the body box. For this thesis research (Chapter Two), the body box was originally designed to house a subject exercising on a small cycle ergometer (Figure A-1), but has since been used in other studies (Chapter Three and Appendix C). Body plethysmography is based on principles derived from Boyle's Law whereby in an airtight space, any volume change is proportional to the change in pressure (West, 1999). Therefore, if a subject is placed inside the box and is breathing to and from the exterior of the box, the change in lung volume with breathing is reflected as a change in pressure within the box. The measured box pressure can be calibrated to a certain change in box volume (as described below).

A.1.1 Design

In order to maximize the sensitivity of the pressure transducers measuring the changes in box pressure, the box was design to be as small as possible, yet adequately fitting the purpose of the study. For a given change in box volume, a large box with a large internal gas volume will give a smaller change in pressure than a smaller box. For example, the box used in this research had dimensions of 2.13 m x 1.22 m x 0.76 m, which created an internal volume of approximately 2700 L. When box volume was calibrated using a standard 3 L syringe, the change in box pressure was less than 2 cmH_2O. It would be expected that the change in box pressure would be much greater for a given change in box volume if internal volume were lower and the sensitivity of the pressure transducers would be greater due to a greater signal to noise ratio. It is imperative, however, that the box be large enough that there is little risk of the subject contacting the walls or ceiling of the box, as any such contact would result in increased levels of box pressure noise.

A.1.2 Construction

The box (Figure A-1) was created out of a combination of 19 mm thick plywood and 13 mm thick plexiglas. The plywood formed the base, ceiling, back wall, and the structure of the remaining walls and door and the plexiglas was used to have several large windows permitting visual contact with the subjects. There were positives and negatives to the use of both plywood and plexiglas in this box. Plexiglas is non-porous, but is more flexible; therefore, it was easy to seal, but would deform quite easily. Plywood is relatively rigid, but is quite porous; therefore, it formed a more solid frame, but much time was needed to make it airtight. The plexiglas door was mounted on steel double hinges (Figures A-1) and was sealed with the use of electromagnets mounted in the door frame and corresponding metal disks mounted on the door. Weather-stripping was used to create the airtight seal surrounding the door frame (Figure A-2).

Several airtight ports were created for connection of the gas collection tubing and the pressure measurement tubing (Figure A-3). Female PVC connectors were embedded in the walls of the box to allow the gas tubing to be connected with male connectors. Several additional PVC connectors were embedded in the walls of the box in case extra ports were required. Pressure measurement tubing was attached to plastic syringe tips embedded into smaller ports in the box walls. As it would have been difficult to cut the required ports into the plexiglas walls after the box was assembled, these ports were created prior to assembly. Once the box was created, the syringe tips and the PVC connectors were secured into their respective ports. A large rubber stopper was placed in each of the unused PVC connectors to in order to seal those ports.

In order to create a sealed airtight box, the plywood walls needed to be painted with several coats of sealant paint. The joints and any knots in the wood needed to be sealed using several layers of caulking. Once it seemed that adequate coverage was achieved, a leak test was performed as follows:

(a) connect a calibrated pressure transducer to the desired port in the box,

(b) connect a 3 L volume syringe to one of the open ports and seal the remainder of the box,

(c) perform one half stroke (3 L) with the syringe to vacate 3 L from the box and to create a negative pressure inside the box. Hold the syringe in this position,

(d) watch and time the change in box pressure over time. The faster the pressure change, the greater the degree of air leak.

(e) keep the syringe in position and vent the box. Reseal the box and inject 3 L into the box to create a positive pressure. Repeat point (d).

The change in box pressure over time can be measured and the time constant calculated. Time constants reflect the amount of time it takes 37% of the total air to leak from the box. Time constants of greater than 30 seconds were considered adequate after comparison to commercialized systems. On initial leak testing after the box was first painted and the joints and knots were caulked, time constants were less than 10 seconds, indicating further air leakage. In order to detect the location of the leaks, the box was pressurized with a blower and painted with a soap solution. The location of the leaks were evidenced by the creation of air bubbles. These locations were marked and were resealed once the box was dry. This process was repeated two additional times before adequate time constants were achieved. Once appropriately sealed, time constants for both positive and negative pressures were greater than two minutes. The leak test was performed during the calibration period preceding each and every experimental test.

Another problem that occurs with body plethysmography is the upward drift in box pressure with the increase in temperature inside the box. A small compensation chamber was created to account for this drift. This chamber was a sealed plexiglas box except for a port for pressure tubing and a port for a 25 gauge needle. The size of the needle was selected so that the relatively slow pressure drift due to temperature changes was equilibrated inside the compensation chamber. The pressure tubing from the compensation chamber was connected to the negative side of the differential pressure transducer such that any change in the chamber pressure would be subtracted from the pressure signal coming from the body box. Therefore, the slow thermal drift was negated from the total pressure signal and the pressure change due to changes in lung volume remained. Based on trial and error, it was found that bigger caliber needles equilibrated too quickly and some of the breathing pressure changes were lost; smaller needles equilibrated too slowly and the thermal drift was not fully subtracted.

A.1.3 Calibration and Validation

Prior to validating the changes in box pressure to lung volume changes, appropriate calibration procedures were established. Calibration will vary depending on the relative size of the subject and all the equipment used, therefore, must be performed in the same conditions as the actual measurements. The subjects were sealed inside the box and were breathing to and from the exterior of the box. A one-minute period of quiet breathing allowed for stabilization of temperature changes inside the box. A 3 L syringe was connected as described above. Subjects were instructed to hold their breath for the duration of the calibration procedure. During the breath hold, 3 L of air was injected and withdrawn from the box using the syringe. In order to account for the slow leak in both the positive and negative directions within the box, the syringe handle was started at approximately 1.5 L during calibration such that there would be an equal displacement of pressure in the positive and negative directions. If the handle position at the start of the test was either fully open or fully closed, the slow leak in the box would drive the mean pressure change toward zero, and the pressure change would drift toward the point of equal displacement. Although the mean pressure change over a single cycle of 3 L calibration would be similar to the procedures used, the degree of error was greater. Varying flow rates were used and the peak to peak pressure change per stroke was measured. The pressure changes were averaged across the entire procedure and that average became the conversion factor to equal 3 L change in box volume. Calibration was always performed prior to each test in each subject in Studies One and Two and verified after testing in each subject in Study One. In Study One, I found that there was always less than a 3% error between the pre-test and post-test calibration.

An essential aspect of the use of the body box was that the volumes obtained are valid measures of lung volume. In order to address this concern, concurrent measurements of lung volume changes were obtained using a dry-rolling spirometer and the body box as part of initial box validation procedures. The spirometer was placed outside of the box and connected to one of the ports in the body box through corrugated breathing tubes and PVC connectors. Subjects sat inside the sealed body box and re-breathed into the spirometer at varying tidal volumes and flow rates. Both the box-measured and spirometer-measured lung volumes were recorded. Three subjects were used and the data combined to confirm box validity. The spirometer volumes correlated significantly with the box volumes ($r^2 = 0.998$; $y = 0.989x + 0.01$). These results demonstrated a high degree of concurrent validity for the box-measured lung volume changes and suggested that the body-box method could be accurately used to determine lung volumes.

A.1.4 Procedural concerns

A.1.4.1 Thermal Drift

Temperature induced drifts in body box volume were a significant concern. The pressure signal obtained with the differential pressure transducer was adequately stabilized with the use of the compensation chamber described above; however, the pressure drift itself was still present. The increase in box pressure generated with a subject exercising in the sealed box was sufficient to separate the magnets of the door, thus venting the box. It was discovered that an exercising subject generates enough heat within the body to increase box pressure to critical levels after only approximately 2 minutes of light exercise in t-shirt and shorts. This problem was compounded with heavier exercise. Therefore, it was only possible to collect volume data within the box for short periods of time. To avoid the potential complication of breaking the door seal, a vent was left open during most of the exercise protocol. This vent was closed for a maximum of one and a half minutes each time pertinent data were collected.

A.1.4.2 Inspiratory Capacity

The body box measures only the change in volume, not actual lung volumes. Thus, tidal volumes could be directly obtained; however, where the tidal volume occurred within each subject's vital capacity was not directly known. Inspiratory capacity (IC) maneuvers were used to estimate the relative placement of lung volumes within the range of physiological volume by tracking the change in end-expiratory lung volume (Babb and Rodarde, 1991). ICs involve inspiring completely to TLC from the EELV at any given point in time and their use depends upon the assumption that TLC does not acutely change with exercise (Stubbing et al, 1980a; 1980b). ICs during exercise have been shown to be reliable in normal subjects (Stubbing et al, 1980a) and in patients with lung disease (Yan et al, 1997). The timing of the instruction to inhale completely is an important criteria for obtaining a direct measurement from EELV to TLC. As it was very difficult to ensure the EELV immediately prior to the IC maneuver was representative of the average EELV for the given exercise condition, it was disregarded. Instead the average of the prior three – four EELVs was used. This factor creates a minor concern related to the ratio between inspired volume and expired volume. At low – moderate intensities of exercise, inspired tidal volume tends to be greater than expired tidal volume, which creates an upward drift in measured volume over time (Johnson et al, 1999). When this drift was present, a correction factor was applied as described by Johnson et al (1999).

A.2 Muscle Fatigue

A.2.1 Definitions and measurement

Muscle fatigue is generally defined as any exercise-induced loss of muscle force or power; however, this loss in muscle function can be due to a reduction in the electrical drive to a muscle (central fatigue), to a reduction in contractile function (peripheral fatigue), or to a combination of both factors (Gandevia, 2001). These definitions are importantly in contrast with the concept of task failure (the point when a particular task is ceased). Although the development of muscle fatigue may cause task failure, this is not always true. Task failure may occur in the absence of muscle fatigue and muscle fatigue may be present after exercise that is not to task failure (Gandevia, 2001). For example, in Study Three (Chapter Four), subjects exercised to whole body task failure, but the presence of muscle fatigue occurred only in subjects who were limited by leg muscle function.

One common measure of generalized fatigue is the use of maximal voluntary isometric contractions (MVICs) to determine pre and post exercise maximal muscle force development (Vollestad, 1997). If muscle fatigue occurs, the post exercise force will be less than the pre-exercise force. There are two major concerns with the use and interpretation of MVICs as a measure of fatigue. First, MVICs require a maximal voluntary effort (Gandevia, 2001). As such, motivation, feedback, and practice are important factors. With MVICs, however, it is difficult to determine whether a reduction in force after exercise is due to muscle fatigue, to inhibitor factors within the central nervous system, or to poor motivation (Vollestad, 1997). Second, MVICs can not determine if the cause of the reduction in force is of central or peripheral origins. MVICs have been shown to be valid and reproducible (Todd et al, 2004), however. Therefore, the use of MVICs as a method of determining the presence or the degree of muscle fatigue is debatable and likely depends upon the question being asked.

A technique that has been recently used to determine the degree, nature, and in some ways the cause of muscle fatigue is the interpolated twitch technique (ITT) (Shield and Zhou, 2004). The ITT involves stimulating, either electrically or magnetically, a motor nerve during a MVIC and measuring the force output of the innervated muscle or muscle group (Gandevia, 2001). An MVIC is performed and, at the plateau in peak force, the nerve is stimulated supramaximally (described below) to produce a twitch force. Any increase in the force output due to the interpolated twitch represents submaximal muscle activation (Gandevia, 2001). When compared to a twitch obtained with a relaxed muscle, the degree of voluntary activation (VA) can be measured as follows: VA = (1 – interpolated twitch/resting twitch). Any reductions in VA during a MVIC post exercise indicates that the motor drive to a muscle or muscle group is impaired (Gandevia, 2001). This technique is an effort-independent method of determining the degree of central fatigue after exercise, however requires the use of a high power output stimulator and very sensitive force measurements (Shield and Zhou, 2004).

As an extension to the ITT, resting potentiated twitches have been used to determine the degree of peripheral or contractile fatigue (Saey et al, 2006; Kufel et al, 2002). As twitch amplitude is highly dependent on the muscle contraction history, the use of a maximal muscle contraction immediately prior to the resting twitch maximally potentiates the twitch amplitude (Kufel et al, 2002). It has been demonstrated that this method is highly reproducible, shows less variability, and is more sensitive to changes in muscle fatigue than the unpotentiated twitch (Kufel et al, 2002). Reductions in potentiated twitch after exercise are most likely due to the presence of low-frequency fatigue, which is known to impair the excitation-contraction coupling in skeletal muscle (Kufel et al, 2002). Therefore, this technique is an effort-independent method of determining the degree of peripheral or contractile fatigue, but requires the same technical equipment as the ITT (Kufel et al, 2002).

In summary, although the use of MVICs can determine the overall level of muscle fatigue, there are limitations to its use and interpretation. Effort-independent techniques such as the ITT and potentiated twitch can provide information related to the degree of central and peripheral fatigue, respectively. The choice of technique depends upon the specific question being asked, as well as the equipment and technical expertise available.

A.2.2 Magnetic stimulation

Interpolated and potentiated twitches have been traditionally performed using electrical stimulation of a motor nerve; however, electrical stimulation can be quite painful, often shows poor reproducibility, and is more challenging to obtain a supramaximal stimulus (Man et al, 2004). Recently, magnetic stimulation has been used as a relatively painless alternative to electrical stimulation (Man et al, 2004). Magnetic stimulation creates intense magnetic fields that produce electrical fields, which will result in depolarization of a motor nerve (an action potential) and create a similar twitch contraction as does electrical stimulation (Man et al, 2004). As well, the magnetic fields preferentially active the larger motor nerve fibres and will avoid the smaller pain-mediating fibres (Man et al, 2004). This method of measuring effort-independent muscle strength and fatigue has been shown to be both valid and reproducible (Polkey et al, 1996) and has been used in recent research in clinical populations (Saey et al, 2006; Mador et al, 2003).

A.2.3 Procedural concerns

A crucial concern in the use of stimulation to produce interpolated and potentiated twitches is the requirement for the stimulus to be supramaximal so that the corresponding motor unit action potiental (M-wave) and muscle force twitch can be deemed truly maximal (Shield and Zhou, 2004). There are several issues related to this requirement. These concerns and issues have been reviewed in detail (Shield and Zhou, 2004); however, the key issues related to the work completed for this thesis are discussed below.

First, the site of stimulation must produce the highest M-wave amplitude possible to ensure that the electrical drive to the muscle is maximal. In the case of quadriceps femoris activation during knee extension, the femoral nerve has been used previously; however, stimulation at this site will also activate sartorius, which may result in a degree of antagonist activation in the direction of knee flexion (Shield and Zhou, 2004). An alternative to femoral nerve stimulation is direct motor point stimulation (Shield and Zhou, 2004). Direct motor point stimulation of the vastus lateralis muscle was used in Study Three (Figure A-4) for several reasons: a) it was found to be more comfortable than stimulation at the femoral triangle; b) access to the femoral triangle may have compromised the patients' sense of privacy; c) the vastus lateralis is the primary quadriceps muscle involved in both cycling and knee extension (Basmajian and DeLuca, 1985) and direct stimulation, therefore, would likely result in greater sensitivity in fatigue measurements. The chance of agonist or antagonist muscle activation is also present with direct motor point stimulation (Shield and Zhou, 2004); however, this concern was deemed negligible as it would have also been present if femoral nerve stimulation was used.

Second, the stimulus must be of sufficient intensity to elicit a maximal muscle contraction (Shield and Zhou, 2004). The twitch and M-wave response to a given stimulus intensity depends upon muscle length, and magnetic coil choice and placement (Man et al, 2004). Supramaximality of the stimulus is determined primarily by the demonstration of a maximal M-wave at submaximal stimulator output intensities (Shield and Zhou, 2004; Gandevia, 2001). In order to demonstrate this finding, a recruitment curve must be created (Figure A-5). The techniques and methods employed in Study Three demonstrated a maximal M-wave response at a mean of 83.4% of stimulator output (range 70 -95%) indicating that the use of 100% would be supramaximal in each subject.

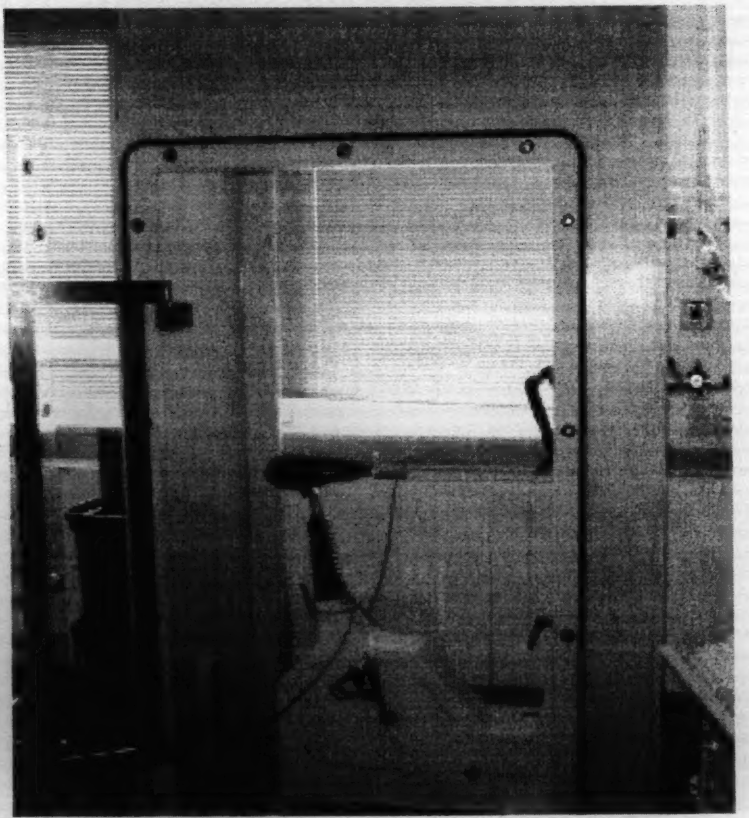

Figure A-1. The body plethysmograph (body box)

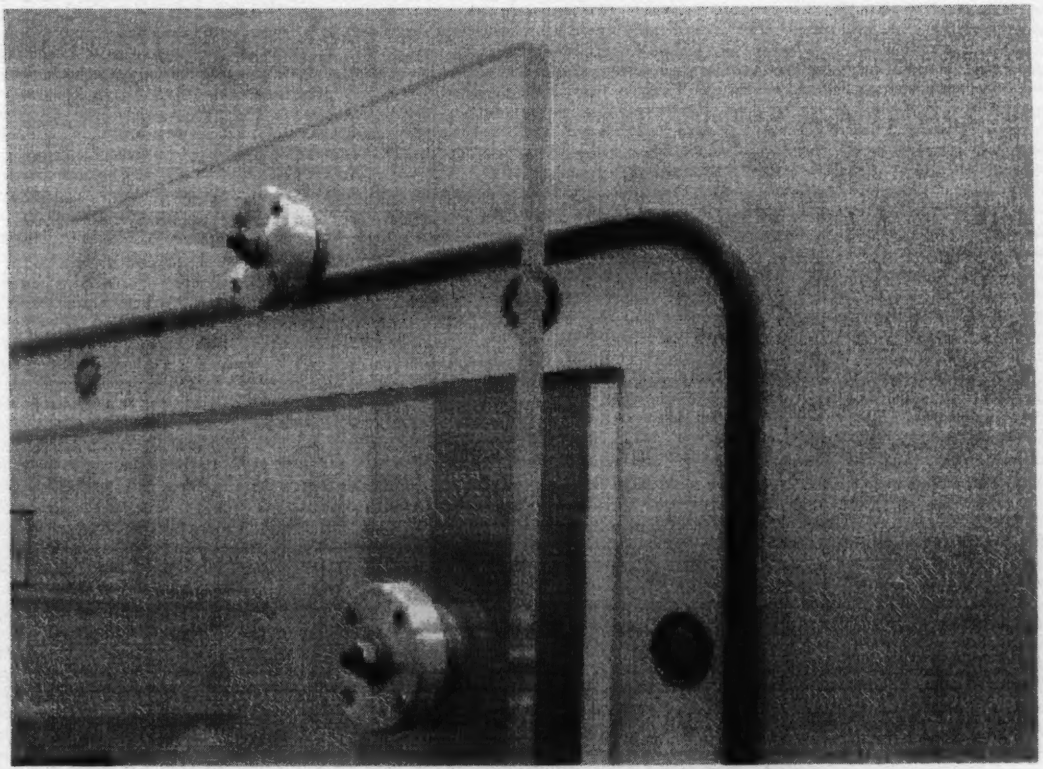

Figure A-2. The electromagnet and weather-stripping seal of the box door

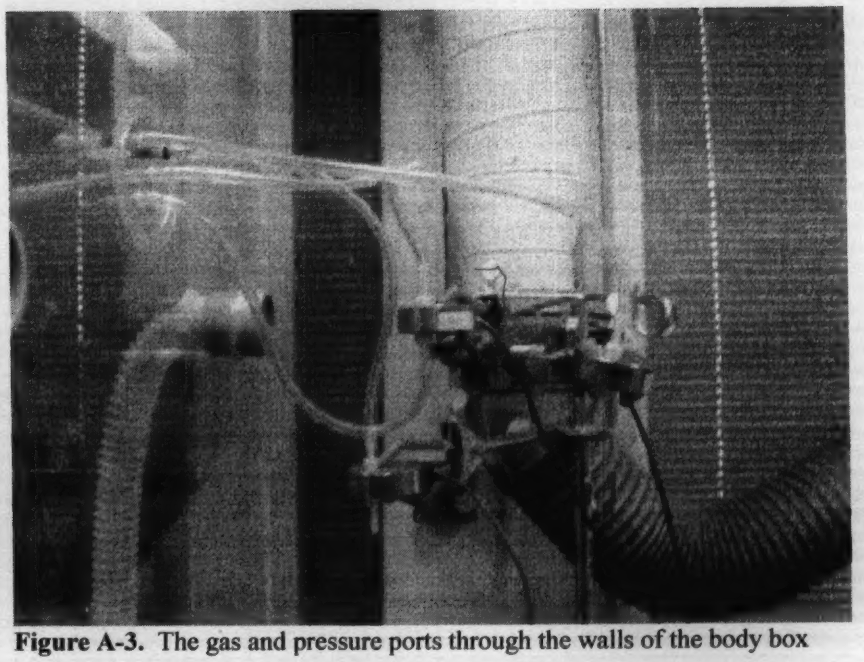

Figure A-3. The gas and pressure ports through the walls of the body box

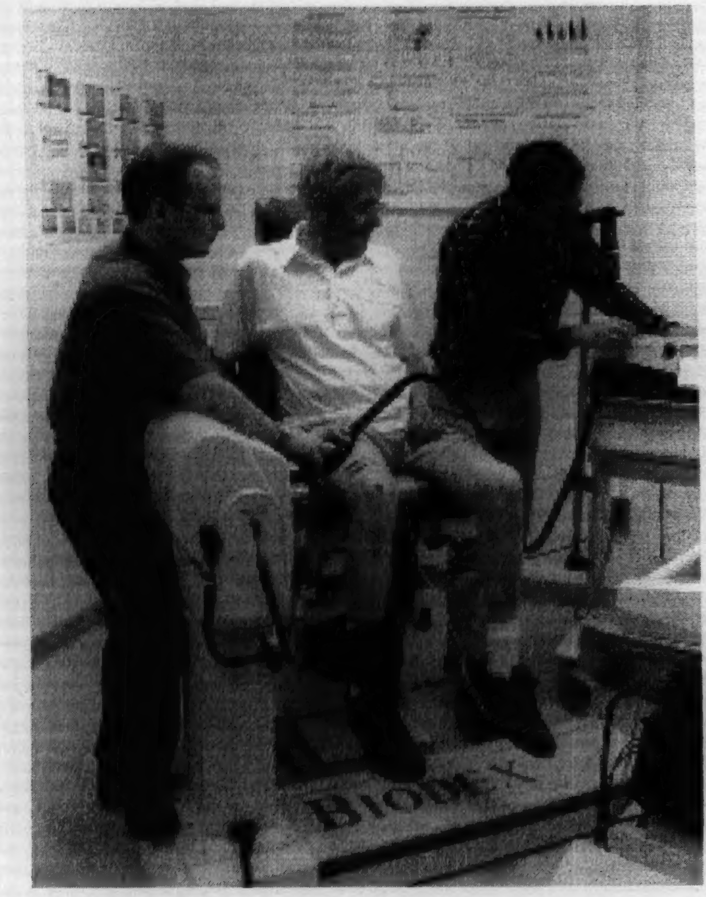

Figure A-4. Interpolated and potentiated twitch measurement in a patient with COPD.

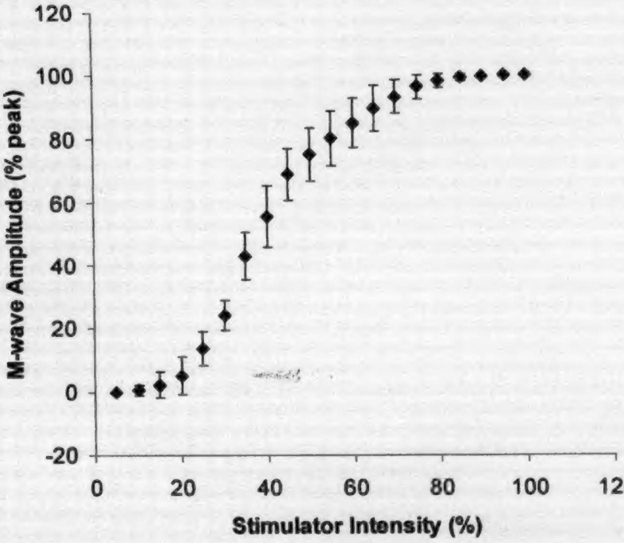

Figure A-5. Recruitment curve during progressive increments in magnetic stimulator intensity

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Appendix B

Additional PhD work

THE IMPACT OF EXERCISE TRAINING INTENSITY ON CHANGE IN PHYSIOLOGICAL FUNCTION IN PATIENTS WITH COPD

B.1 Introduction and statement of purpose

There is little doubt that endurance exercise training is beneficial for patients with chronic obstructive pulmonary disease (COPD) (American Thoracic Society, 1999). Recent research has demonstrated positive effects of exercise training on exercise capacity, symptoms of dyspnea, and quality of life (Noseda et al, 1994; Ries et al, 1987). Endurance exercise appears to have the greatest body of evidence supporting its use when compared to other forms of exercise training such as resistance training or ventilatory muscle training.

It is common practice in many pulmonary rehabilitation programs to prescribe endurance exercise based on patient tolerance (Casaburi et al, 1993). That is, COPD patients will be told to exercise at a moderate level of exertion and to increase exercise intensity as tolerated. There have been recent efforts to quantify exercise intensity to aid in standardizing exercise prescription for COPD patients (Casaburi et al, 1991; Vogiatzis et al, 2002; Giminez et al, 2000). The problem associated with this approach to exercise prescription in this population is that for many years it was believed that COPD patients were only limited by their ability to adequately increase ventilation to match the demands of exercise and, thus, exhibit a ventilatory limitation to exercise (Wasserman et al, 2002; 1991). Only recently, researchers have identified evidence that factors other than ventilation limitation can be very important in limiting exercise. Patients with COPD exhibit several peripheral muscular, cardiac, hemodynamic, and metabolic deficiencies that contribute to exercise limitation (Nici, 2000; Maltais et al, 1998; Simon et al, 2001).

This multifactoral exercise limitation presents a very complex problem when attempting to standardize exercise prescription for these patients. For any given patient, it is very difficult to predict what percentage of peak work rate corresponds with an appropriate exercise intensity. If a limitation to ventilation occurs prior to reaching a maximal cardiovascular response, peak work rate will likely be abnormally low (Aliverti and Macklem, 2001). Therefore, it will be difficult to apply standard exercise prescription principles to these patients.

Previous studies have typically used traditional exercise prescription principles based upon cardiovascular training guidelines to define exercise intensity (Rooyackers and Folgering, 1998; American College of Sports Medicine, 2000). Only recently have we seen an emergence of evidence that implies that because COPD patients are limited by unique factors, they should be prescribed exercise differently than other populations (Casaburi, 2003; Saey et al, 2003;

O'Donnell et al, 2001). In fact, most pulmonary rehabilitation programs still use exercise intensities of 'moderate' and 'as tolerated'. New research, however, has begun to use better defined exercise intensities higher than have been used previously (Casaburi et al, 1997).

The purpose of this review is to examine the current evidence regarding the acute and chronic physiological effects of exercise at varying exercise intensities in patients with COPD. Current concepts and ideas regarding the relationship between exercise limitations and exercise training intensity will be presented.

B.2 Literature Review

Exercise responses and limitations to exercise capacity in patients with COPD

In order to obtain a succinct understanding of exercise training principles in the rehabilitation of patients with COPD, it is important to understand the acute responses and the limitations to exercise exhibited by these patients. As such, several key concepts and new ideas will be examined and presented. A thorough review of these responses and limitations is beyond the scope of this article and several recent reviews can provide more depth for the interested reader (Casaburi, 2001; Nici, 2000; Aliverti and Macklem, 2001; Sietsema, 2001).

The relationship between oxygen consumption and exercise performance in patients with COPD

Maximum oxygen consumption (VO_{2max}) is considered to be the present "gold standard" for measurement of cardiovascular fitness and is a useful parameter for determining aerobic capacity (American Thoracic Society, 2003).

In patients with COPD, average VO_{2max} ranges from 0.5 to approximately 1.6 L/min in most exercise tolerance studies (Oelberg et al, 1998; Jobin et al, 1998; Carter et al, 2003) with peak work rates of only 60 – 120 watts (Maltais et al, 1998; Matthews et al, 1989). Although VO_{2max} is not adequately explained by measures of lung function, VO_{2max} is typically lower in patients with more severe disease (Lewis et al, 1994). However, there is considerable variability in VO_{2max} and exercise performance between patients, suggesting that when comparing patients of similar severity of lung dysfunction, factors other than VO_{2max} are more important in determining exercise performance (American Thoracic Society, 2003). During incremental exercise, the rise in VO_2 with increasing work rates appears to be relatively normal (Sietsema, 2001; Lewis et al, 1994), however, there is often a higher resting VO_2 in more severe patients, reflecting the increased ventilatory cost of breathing (Levison and Cherniak, 1968).

VO_2 is determined by cardiac output (heart rate and stroke volume) and oxygen extraction at the tissue level (Brooks et al, 2000). Systemic oxygen extraction is not normally considered to be a major limiting factor in patients with COPD, but has been found to be reduced in some patients (Oelberg et al, 1998), and not in others (Maltais et al, 1998). Cardiac output and stroke volume are reduced at peak exercise likely due to a reduction in peak work rate occurring because of other limitations (such as ventilatory, muscular or symptom limitations), and not due to a primary limitation in cardiac output (Nici, 2001; Sietsema, 2001). Peak heart rate is usually reduced, especially in studies using patients with more severe COPD (Maltais et al, 1998; Simon et al, 2001). If cardiac output were the primary limiting factor to exercise, one would expect a maximal or near maximal heart rate at peak exercise. Because this does not occur, exercise ceases prior to attaining a maximal, limiting cardiac output. Submaximal cardiac output, on the other hand, appears to be normal (Sietsema, 2001), with the decreased stroke volume being offset by an increased heart rate. Reduction in stroke volume at all exercise intensities is a consistent finding in most patients with COPD (Sietsema, 2001). This reduction is primarily due to reductions in right ventricular output due to lung hyperinflation, increased pulmonary vascular resistance, and reduced venous return owing to increased intrathoracic pressure (Sietsema, 2001). The effects of lung disease on right ventricular dysfunction also extend to the left ventricle. Increased right ventricular pressure and volume induce a septal shift, which reduces left ventricular filling (Sietsema, 2001). The overall effect is reduced left ventricular stroke volume.

Neder et al. found that patients with COPD are typically able to sustain relative constant load work rates that are much higher (82%) than healthy subjects (68%) when expressed as a percent of peak work rate obtained on an incremental test to exhaustion (Neder et al, 2000). They also found that the sustainable work rate achieved (critical power) in patients was directly related to measures of ventilatory function and dyspnea (Neder et al, 2000). The fact that the relative critical power is much higher in patients is likely reflective of an abnormally low peak work rate during the maximal test. This fact provides further evidence that VO_{2max}, and therefore maximal cardiac output, are not likely attained in patients, and suggests that symptoms or limitations in ventilation determine both the critical power and the duration of exercise in work rates above the critical power (Neder et al, 2000).

Exercise limitations in patients with COPD

Much attention has been given in recent literature to determining the limitations to exercise capacity in patients with COPD. Several excellent reviews of both traditional and contemporary views have been published (Wasserman and Casaburi, 1991; Nici, 2000; Aliverti and Macklem, 2001; Casaburi, 2001). A summary of the key determinants of exercise intolerance in patients with COPD is presented in Figure B.1. Traditionally, it was believed that a ventilatory limitation to exercise was the primary and most important cause for exercise intolerance in these patients. A corollary to this belief was the belief that ventilatory limitation to exercise as well as dyspnea precluded the activation of peripheral muscle to sufficient degree to adequately achieve physiological benefit (Casaburi, 2003). It was assumed that the increases in exercise tolerance following exercise training were purely due to psychological factors such as desensitization to dyspnea and an overall feeling of accomplishment (Killian, 1993). Only recently have we known that even low intensity exercise does produce a physiologic training response (Casaburi et al, 1991. The realization of this fact has led to a large number of investigations and speculations related to the 'true' cause of exercise limitation in these patients. This section will deal primarily with the physiologic limitations to exercise, outside of dyspnea. The authors recognize however, that dyspnea remains an important symptom affecting acute exercise tolerance, as well as long term activity level, as shown in Figure B-1.

Ventilatory Limitations

Exercise ventilation in patients with COPD, as in healthy subjects, is a direct consequence of the metabolic demands of exercise (Wasserman and Stringer, 2002). However, a greater minute ventilation is required to achieve a given level of alveolar ventilation. This greater ventilation is due primarily to an increase in the physiological dead space and the resulting ventilation-perfusion mismatch (Wasserman and Stringer, 2002). The result is a reduction in the ventilatory efficiency as indicated by a high V_E/VO_2 or V_E/work rate (Lewis et al, 1994). Peak exercise ventilation, however, is decreased (Matthews et al, 1989). This reduction at peak exercise reflects the reduction in total work rate and has been attributed to a reduced ventilatory capacity or ceiling (Wasserman and Stringer, 2002). There are also significant differences in the way that ventilation is achieved. Patients tend to increase tidal volume to only approximately the volume equivalent to their FEV_1 and this increase occurs early in exercise (Matthews et al, 1989). The major increase in ventilation later in exercise occurs due to a disproportional increase in respiratory rate (Matthews et al, 1989). However, because peak respiratory rate is only slightly greater than normal and there is a marked reduction in peak tidal volume, the net effect is an overall reduction of peak ventilation (Matthews et al, 1989).

The traditional view of ventilatory limitation to exercise is that a combination of a reduced ventilatory capacity and an increased ventilatory demand result in an eventual 'ceiling' effect. That is, the inability to adequately increase ventilation to meet the metabolic demands of exercise was thought to be due to a reduced maximal potential for ventilation (Wasserman and Stringer, 2002). Ventilatory demand is measured by an increasing minute ventilation (V_E) with exercise and ventilatory capacity is most frequently measured by maximal voluntary ventilation (MVV), or surrogates of MVV such as FEV_1 x 35 or 40 (American Thoracic Society, 2003). The closer V_E approaches MVV, the greater the chance of a ventilatory limitation to exercise. Problems with this approach were identified as it became apparent that measures of resting lung function do not correlate well with ventilatory patterns during exercise (O'Donnell, 2001; Johnson et al, 1999). Recently, other measures of ventilatory limitation have been discussed (Wasserman and Stringer, 2002; O'Donnell et al, 2001; Johnson et al, 1999), but a consensus regarding the most appropriate measure has yet to be reached.

One such measure is the determination of inspiratory capacity during exercise (O'Donnell et al, 2001). Inspiratory capacity is an easy, non-invasive method of determining the degree of dynamic hyperinflation that occurs in patients with COPD (O'Donnell, 2001). Dynamic hyperinflation seriously affects ventilatory mechanics, inspiratory muscle function, and cardiac function (O'Donnell, 2001). As ventilation increases, end expiratory lung volume increases (dynamic hyperinflation), which, in turn, decreases the potential increases in tidal volume (O'Donnell, 2001). As we know that total lung capacity does not increase with exercise (Wasserman and Stringer, 2002), tidal volume can only increase to the volume that inspiratory capacity allows (O'Donnell, 2001). Thus, a reduced ventilatory capacity is more a rising 'floor' than a low 'ceiling'. The degree of dynamic hyperinflation correlates very well with exercise tolerance (O'Donnell et al, 2001; Marin et al, 2001) as has been demonstrated in both maximal (O'Donnell et al, 2001; Diaz et al, 2000) and submaximal (Marin et al, 2001) exercise. Dynamic hyperinflation is also associated with increasing sensations of dyspnea (Marin et al, 2001) and an increased work of breathing (Sliwinski et al, 1998). Although examination of dynamic hyperinflation is emerging as a promising method of determining ventilatory limitations to exercise, the exact measurement and interpretation of when a true limitation occurs has yet to be demonstrated.

Cardiac Limitations

As discussed above, although a patient's ability to maximize cardiac output, and thus VO_2, is impaired, it is unlikely that these factors constitute a primary limitation to exercise. Reductions in peak cardiac output likely reflect a lower attainable work rate due to increasing dyspnea, ventilatory limitation, or other limiting factors. This finding has significant implications for exercise prescription, as will be discussed later.

Peripheral Muscle Limitations

Recent evidence has pointed to skeletal muscle dysfunction as a potential limiting factor to exercise tolerance in patients. Documented skeletal muscle abnormalities that affect exercise performance in patients with COPD include: decreased lower extremity skeletal muscle mass (American Thoracic Society, 1999), strength (Bernard et al, 1998), endurance (Serres et al, 1998), capillarity (Jobin et al, 1998), muscle oxidative enzyme capacity (Maltais et al, 1996), proportion of type I fibers (Jobin et al, 1998); and a rise in the proportion of type II fibres (Jobin et al, 1998). The net effect of these abnormalities is a greater dependence upon anaerobic metabolism, an early rise in lactate during low levels of exercise (Maltais et al, 1998; 1996), and a markedly reduced lactate threshold (Casaburi et al, 1991; Zacarias et al, 2000). There is also direct evidence that skeletal muscle strength is correlated with exercise tolerance (Gosselink et al, 1996) and that skeletal muscle training increases exercise tolerance (Troosters et al, 1996). As well, administration of a bronchodilator (which increases FEV_1 and raises the potential to increase ventilation) does not improve exercise tolerance in all patients (Saey et al, 2003). After exhausting exercise, contractile fatigue of the quadriceps occurs in some patients, limiting exercise tolerance (Saey et al, 2003). These findings together provide evidence that skeletal muscle abnormalities contribute to exercise limitation in certain patients and may be due to any combination of deconditioning, muscle wasting, malnutrition, corticosteroid myopathy, hypoxia, or electrolyte disturbances (Maltais et al, 2000; Casaburi, 2001).

Limitations to Oxygen Delivery

Almost forty years ago, Levison and Cherniack (1968) found that during exercise, respiratory muscle oxygen consumption required approximately 40% of the total body VO_{2peak} in patients with COPD compared with 10 –15% in healthy controls. They speculated that this increased respiratory requirement would reduce the available oxygen for the exercising leg muscles and this would lead to early exercise limitation (Levison and Cherniak, 1968). Recently, it has been found that increasing respiratory muscle loads during exercise reduces exercise performance and leg blood flow at maximal exercise in healthy subjects (Harms et al, 1998; 1997). In some patients with COPD, a plateau in leg muscle blood flow, oxygen delivery, oxygen consumption, and oxygen extraction occurs during incremental exercise, despite further increases in work rate and whole body VO_2 (Maltais et al, 2001; 1998; Simon et al, 2001). Although this plateau is present in healthy subjects, it occurs at a much lower work rate in patients (Wasserman and Stringer, 2002). It was speculated that increases in work of breathing in the patients who did demonstrate a plateau might be a reason for reductions in exercise tolerance in these patients, and that this may be due to redistribution of blood flow to the respiratory muscles during exercise (Simon et al, 2001). As well, when reducing the effect of central cardiorespiratory limitations during whole body exercise through the use of heliox and hyperoxia, a significant metabolic reserve is demonstrated in skeletal muscle of patients with COPD (Richardson et al, 1999). This reserve disappears when performing single limb exercise (repeated knee extension) with heliox and hyperoxia. It is likely that this finding demonstrates that skeletal muscle may not be the cause of exercise limitation (Richardson et al, 1999), but that a deficiency in the oxygen delivery system is. As well, it is quite possible that a limitation in oxygen delivery is partly responsible for some of the skeletal muscle abnormalities demonstrated in these patients.

Although the exact mechanisms of exercise intolerance vary across individuals, most patients with COPD come very close to reaching (if not reach) their pulmonary mechanical limits during heavy exercise. Other limitations, such as peripheral muscle fatigue may occur prior to reaching a ventilatory limitation, however; ventilation is usually close to maximal (Saey et al, 2003; O'Donnell et al, 2001). Importantly, however, these limitations appear to be different than healthy age matched control subjects in type and magnitude, making exercise prescription much more complex.

B.3 Concepts relating exercise limitation and exercise training intensity in patients with COPD

In patients with COPD, because heart rate and VO_2 do not usually reach a true maximum during incremental testing, prescribing exercise intensity using a standard percentage of maximal heart rate or VO_{2max} work rate is unwarranted. A percentage of peak exercise capacity commonly used in healthy subjects will underestimate the desired training intensity for patients, as can be inferred from the Neder et al study mentioned above (Neder et al, 2000). Therefore, it is inappropriate to use published guidelines (% of heart rate max or VO_{2max}) for exercise prescription that are based on knowing or predicting a maximal cardiovascular response (as in healthy subjects).

It is possible, however; that heart rate could be used as a marker of training intensity, rather than as a method of prescribing intensity. That is, once a given intensity (in work rate) has been selected, it is possible that heart rate may be used to ensure consistent exercise effort. Simmons et al.found that the heart rate response to a given level of work was predictable during incremental exercise (Simmons et al, 2000). However, Zacarias et al. (2000) found that due to the high intersubject variability in heart rate at a standard physiological time point, the use of heart rate targets is unadvised for prescribing routine exercise in patients. As well, Brolin et al. (2003) found that at moderate intensity exercise, heart rate increased over time independently of work rate. These findings support clinical observations that the use of heart rate for exercise prescription is not reliable.

If VO_2 and heart rate should not be used to set intensity guidelines, intensity must be set in other ways. As pointed out by Maltais et al (2001), exercise capacity can often be limited by perceptions of dyspnea and fatigue without evidence of a true physiological limitation. Horowitz and Mahler (1998) demonstrated that patients can reliably reproduce a standard exercise intensity by the use of dyspnea ratings at moderate to high intensities, but not at lower intensities (Horowitz and Mahler, 1998). As well, this relationship is stable between exercise modalities (cycle and treadmill) and stable over time with exercise training indicating that monitoring dyspnea may assist in setting exercise intensity (Gimenez et al, 2000). However, in situations where the work rate is known (cycle ergometry and treadmill exercise), it is likely more accurate to actually use desired work rate, rather than a marker such as heart rate or dyspnea. However intensity is determined, it is still unclear what intensity to use for prescription. The remainder of this review will examine the physiological outcomes of training at various exercise intensities to assist in determining the most appropriate exercise intensities in patients with COPD.

B.4 Outcomes after various intensities of exercise training and current recommendations for training intensity in patients with COPD

Current recommendations for training intensity

Several recent sources have cited guidelines for exercise training intensity in patients with COPD (American Thoracic Society, 1999; Casaburi, 2001; Cherniak, 1999; American College of Sports

Medicine, 2000). At present, however, most guidelines are relatively vague and non-specific. One reason for this is a continued reliance in many pulmonary rehabilitation programs on prescribing and progressing exercise using the guideline of 'as tolerated.' (Casaburi, 2001; Cherniak, 1999). As patients most commonly describe severe symptoms of fatigue and shortness of breath as the 'limits' to their exercising abilities, it is easy to simply tell patients to exercise at a level to which they are capable. Although this approach will induce some physiological change (Casaburi, 1993), it will not ensure optimal physiological benefit. Prescribing exercise based on subjective levels of tolerance is conducive to gaining confidence in exercise, and is likely appropriate as an initial guideline for exercise prescription.

A second reason for a lack of concrete guidelines for training intensity is the fact that it is only recently that researchers have documented that true physiological benefits from exercise are actually possible (Casaburi et al, 1997; 1991). Some general information currently exists, but more research is required to better attain the level of specificity of physiological exercise prescription guidelines that is seen in healthy populations such as athletes. This section will outline exercise intensity guidelines currently recommended. A detailed discussion of different intensities will follow in the subsequent sections.

One of the primary sources of specific exercise prescription guidelines in North America is the ACSM. The ACSM in their 2000 edition of *Guidelines for Exercise Testing and Prescription* (2000) recognize the lack of a consensus for optimal training intensity in patients with COPD. However, they have adopted the potential use of two strategies used in the literature. The first, as described by Ries et al (1987), advises exercise at 50% of VO_{2peak}, which is a similar strategy as is used in healthy older adults. This lower to moderate intensity should enhance adherence and reduce the risk of injury, while still achieving significant benefit (American College of Sports Medicine, 2000). The second strategy, as described by Punzal et al (1991) is to exercise patients to the maximal limits tolerated by symptoms. As mentioned previously, patients with COPD can sustain higher relative intensities of exercise (as determined by percent of peak work rate) than healthy older adults (Neder et al, 2000) and are able to increase the duration of exercise over time (Ries et al, 1987). Although it is recognized that higher intensity exercise (~80% of peak work rate) should lead to greater benefit, this may be at the expense of compliance and adherence (Casaburi, 2001).

In 1999, the American Thoracic Society (ATS) published an official statement on pulmonary rehabilitation (1999), which also recognizes that evidence of different exercise protocols is emerging, but that at the present time, it is insufficient to provide guidelines. They recommend a target intensity of 60 - 80% of peak VO_2 or work rate, but concede that, in clinical situations, heart rate and dyspnea ratings can also be used to monitor intensity. They also state that, for patients who are unable to sustain exercise at this intensity, shorter periods of intermittant training may be used at intensities of 60 – 80% with alternating periods of two to three minutes of exercise and rest (American Thoracic Society 1999).

Obviously, there are no standard physiologically based guidelines for exercise intensity prescription that are specific to patients with COPD. Other guidelines, as produced in pulmonary rehabilitation texts (Casaburi, 1993; Cherniak, 1999) follow similar patterns or simply state 'as tolerated'. As such, there is wide variety in the intensities used in research related to outcomes of training programs for these patients.

Physiological outcomes of COPD exercise training related to prescribed exercise intensity

It is clear that exercise training exerts a positive benefit on patients with COPD. Until relatively recently, this benefit was believed to be primarily psychological (Casaburi, 2001). Any increases in physiological parameters were simply due to reductions in shortness of breath that allowed a greater workload (Casaburi, 2003). While reductions in shortness of breath due to exercise training do seem to allow greater workloads during exercise testing (Maltais et al, 2001), it is now clear that there are very concrete physiological benefits to exercise training as well (Casaburi, 2003). This section will review recent research examining different physiological benefits to endurance exercise training in patients with COPD. As well, the impact of different training intensities will also be assessed.

For the purposes of classifying studies into categories of intensity for this review, low intensity is considered to be less than 70% of peak work rate, VO_2, or heart rate, as applicable; moderate, between 70 and 79%; high, between 80 and 89%; and near maximal, 90% or above. This classification system rates exercise intensity higher than has been used previously (American College of Sports Medicine, 2000). As patients with COPD are markedly limited in exercise tolerance, simple activities of daily living such as sweeping represent high percentages of peak work rate (Vellos et al, 2003). Most exercise studies in patients with COPD have used intensities of exercise well above what would be considered moderate, and, as proposed above, peak exercise tolerance likely does not represent a true maximal cardiovascular capacity. Therefore, classification of low and moderate intensity exercise has been represented by percent intensities higher than previously used.

All of the studies reviewed found that exercise training exerts a physiological benefit; however, the benefits described are as varied as the protocols used for testing, training, and recruitment. Training was prescribed anywhere from 2 – 6 times per week, at intensities of 40 – 100% of peak exercise workload, for 20 – 60 minutes of continuous or intermittent exercise, and lasting 3 to 12 weeks. As well, patients with a wide range of disease severity were assessed. In general, the most common finding was a significant increase in work rate on incremental testing. Increases in work rate were between 7 and 35% over the training period (Otsuka et al, 1997). Increases in work rate also appear to be one the variables most affected by training intensity (Otsuka et al, 1997; Gigliotti et al, 2003; Casaburi et al, 1997). Significant variations occurred in low to moderate workrates (40 – 80% of peak) that do not appear to be related to actual training intensity. Increases at this level ranged from 7 to 33% from pre training to post training (Otsuka et al, 1997; Ries et al, 1995). High to near maximal training intensities (80 – 100% of peak), however, produced more consistently greater increases in pre to post training work rate, ranging 23 to 37% (Gigliotti et al, 2003; Casaburi et al, 1997).

Increases in endurance time and timed walking distance are also quite common. Increases in time to fatigue at identical pre and post training work rates range from 70 – 100% (Ries et al, 1995; Patesso et al, 1992; Puente-Maestu, 2003); however, these increases do not seem to be affected by training intensity. It should be noted, however, that the intensity of the endurance tests used to measure time to fatigue seemed to closely resemble the training intensities. A greater increase in endurance time might be expected when testing at an intensity that is lower than training intensity (Casaburi et al, 1991).

Increases in peak oxygen consumption are not as commonly observed. Many low and moderate intensity studies show non significant increases or even decreases in VO_{2peak} after training (Bernard et al, 1999; Clark et al, 1996). High to near maximal intensity studies tend to show more consistent increases in VO_{2peak} (Maltais et al, 1997; Ries et al, 1987); however, these increases are often much lower than the average 20% increase (Brooks et al, 2000) expected for healthy subjects, ranging from 5 – 16% (Casaburi et al, 1997; Vogiatzis et al, 1999). Three studies found increases that paralleled those seen in healthy subjects (20 – 30%), but all three used subjects that were younger (48 – 55 years), and had less severe COPD (FEV_1 1.58 – 1.87 L or 54 – 56% of predicted) (Casaburi et al, 1991; Gimeniz et al, 2000; Vallet et al, 1997). It is likely that, from an exercise limitations point of view, that there is a continuum of age and disease severity in which patients that are younger and less severe will exhibit limitations that are more similar to those of healthy subjects than those exhibited by older, more severe patients. It follows, then, that the relative benefits to exercise will more closely approximate those seen in healthy subjects when patients are not constrained by more severe dyspnea, ventilatory limits, deconditioning, and muscle dysfunction. Peak heart rate seems to increase from 0 – 7% (Casaburi et al, 1997; Gigliotti et al, 2003; Vogiatzis et al, 1999), whereas, oxygen pulse increases 16 – 19% (Vallet et al, 1997; Gimeniz et al, 2000). Also, significant decreases (5 – 13%) in submaximal heart rate at a given work rate are frequent (Maltais et al, 1997), and likely indicate greater training efficiency, and higher stroke volume for a given VO_2 (McArdle et al, 2000).

Interestingly, peak ventilation also increases with training (6 – 11%), with slightly greater change likely after higher intensities of training (9 – 11%) compared with lower intensities (6 – 8%) (Gimeniz et al, 2000; Casaburi et al, 1997; Vogiatzis et al, 1999; Serres et al, 1997), although this is not consistent across all studies. Greater peak ventilations may be explained by reductions in dynamic hyperinflation and by increases in ventilatory efficiency that occur due to training (Gimeniz et al, 2000).

As anaerobic threshold is difficult to measure with certainty in patients with COPD, the effects of training on anaerobic threshold are unclear. However, the studies that have examined anaerobic threshold have found increases of between 0 and 50% with greater apparent increases in the studies using higher intensity exercise (Gimeniz et al, 2000; Maltais et al, 1996), albeit with considerable variability. Accordingly, the response of lactate to exercise is also improved with training (Casaburi et al, 1991; Puente-Maestu et al, 2003). Maximal lactate at peak exercise increases (approximately 36%) (Casaburi et al, 1991) after high intensity training, but less (0 – 17%) with low to moderate intensity training (Puente-Maestu et al, 2003; Maltais et al, 1996). Increases in maximal lactate production likely reflect a greater work rate achieved during testing, and therefore, more muscle activation. Lactate production is reduced significantly at submaximal work rates, following a similar pattern (30 – 36% with high intensity training and 0 – 30% with low to moderate intensity training) (Casaburi et al, 1991; Puente-Maestu et al, 2001).

The changes in anaerobic threshold and lactate production are likely due to improvements in skeletal muscle aerobic capacity in response to moderate intensity exercise training. Skeletal muscle oxidative enzyme activity increases by 15 – 40% (Maltais et al, 1996). VO_2 kinetics during constant work rate exercise increase by 16 –18% (Otsuka et al, 1997; Puente-Maestu et al, 2003) and recovery of muscle oxygenation increases by 16 – 27% (Puente-Maestu et al, 2003). Changes in recovery kinetics have been shown to be associated with changes in oxidative enzyme activity and increases in endurance time (Puente-Maestu et al, 2003).

Differing physiological benefit in studies comparing exercise intensities

There have been very few well designed studies that have directly compared the physiologic benefits of different exercise intensities. As outlined above, even low intensity exercise produces significant physiological adaptations in many measures. Small changes in work rate, heart rate, ventilation, and even VO_{2peak} and anaerobic threshold may be observed (Vogiatzis et al, 1999). However, there are several variables that seem to respond more favorably to higher intensities of exercise. This section will outline the main differences in physiological outcomes observed after different training intensities, and will summarize the results of recent studies.

Only one study was found that compared moderate intensity training with low intensity training. Puente-Maestu et al. (2000) compared the effects of a supervised treadmill training program with a self-monitored walking exercise program in thirty-five patients with COPD (FEV_1 41% of predicted) (Puente-Maestu et al, 2000). Although the initial goal of the study was to have patients exercising at relatively equal intensities, the supervised training group exercised at an intensity of approximately 70% of VO_{2peak} or 70W (moderate), and the self-monitored group exercised at a significantly lower intensity (35W). Peak exercise responses (treadmill) and gas exchange kinetics on an 80% peak constant work rate (cycle ergometer) test were evaluated. Both groups exhibited significant decreases in the mean response time for achieving steady state VO_2 and heart rate, but only the supervised group also had decreases in ventilation and VCO_2 mean response times. As well, only the supervised group increased VO_{2peak}. Only the moderate intensity training group decreased submaximal ventilation rate, which was associated with reduced VCO_2, and that this is not task specific (treadmill or bicycle) (Puente-Maestu et al, 2000).

A well designed study comparing high intensity training with low intensity training was performed by Casaburi et al. (1991). In this landmark study, 19 patients were randomly assigned to a high or a low intensity training group. Each subject performed maximal cycle ergometry testing as well as two constant work rate tests at 50% of peak work rate (or work rate corresponding with 90% of the anaerobic threshold if identified), and at 80% peak work rate (or 60% of the difference between the anaerobic threshold and peak work rate). The high intensity training group exercised at the work rate corresponding to the 80% constant work rate test and the low intensity group trained at the 50% peak work rate test level.

After eight weeks of training, the high intensity group showed significant increases in VO_{2peak} and constant work rate exercise time, and reductions in high intensity constant work rate lactate, ventilation, VO_2, VCO_2, heart rate, and increases in ventilatory efficiency, whereas the low intensity group showed a significant but lesser reduction in lactate only. In the low intensity test, both groups reduced lactate, but only the high intensity group reduced heart rate and ventilation. During incremental testing, both groups increased lactate threshold, but the high intensity group more so (24%) than the low intensity group (11%). The most striking finding, and the one that has guided many more recent studies, is the fact that patients accumulated lactate at very low work rates, and exhibited significant physiological adaptation to training (Casaburi et al, 1991). This study was one of the first to document true physiological adaptation to training in patients with COPD.

Near maximal intensity exercise training is also effective in eliciting physiological benefit. The major significance of this finding is that all such studies reviewed used interval training to achieve near maximal intensity exercise. Many studies using low to moderate intensity continuous training have allowed patients to take a number of rest breaks 'as required', however, the reason for that type of intermittent training is to allow patients some symptom relief before continuing continuous exercise. The interval training used in the near maximal intensity training studies was employed for the purpose of attaining a higher work rate to attempt to elicit greater physiological benefit while still allowing for recovery between exercise bouts (Coppoolse et al, 1999). Although true interval training in patients with COPD may serve to reduce symptoms during exercise (Vogiatzis et al, 2002), the goal of attaining higher work rates may be more important physiologically. Further discussion related to the utilization of interval training in these patients will be presented later.

Coppoolse et al. (1999) studied the effects of eight weeks interval training versus continuous exercise training in twenty-one male patients with severe COPD (FEV_1 37% of predicted). The continuous training group performed cycle ergometry exercise for 30 minutes five days per week at a work rate of 60% of peak work rate achieved on a maximal incremental test. The interval training group (n=10) performed interval training on three days per week that consisted of nine intervals of one minute at 90% of peak work rate and two minutes at 45%, plus a three minute warm up at 60%. The total exercise duration equaled 30 minutes per session and the total average work rate was equivalent to 60% of peak. On the other two days per week, the interval training group performed 30 minutes of continuous exercise at 60%.

After training, only the continuous group significantly increased VO_{2peak} (17%) and decreased ventilatory equivalents for oxygen and carbon dioxide. At peak, however, only the interval group significantly increased work rate, work efficiency, and perceptions of leg fatigue. Both groups increased respiratory muscle strength, but the interval training group more so. There were non significant trends for reduced symptoms of shortness of breath in both groups. At a 45% peak constant work rate test, both groups reduced lactate accumulation, but the continuous group more so. These results are not unexpected given that the interval training may have elicited greater anaerobic adaptations and greater muscular strength and efficiency, and the continuous training may have elicited greater aerobic adaptations. The authors suggest that greater muscular adaptations may occur after interval training, but that oxidative capacity is likely increased more after continuous training (Coppoolse et al, 1999).

In contrast to Coppoolse, Gimenez et al. (2000), found significant aerobic and anaerobic adaptations to daily interval training for six weeks. They randomized 13 younger male (49 years) patients with mild to moderate COPD (FEV_1 = 1.6L) to either an interval training group (n=7) or a continuous walking group (n=6). The interval training group trained on a cycle ergometer for intervals of one minute at 100% of VO_{2peak} achieved on an incremental test and four minutes at 40% peak, for an overall training time of 45 minutes. The average work rate was, therefore, 52% of peak. The continuous training group walked while pushing oxygen carts for 45 minutes and were encouraged to complete the 45 minutes without rest and to increase walking speed. After training, the only significant adaptation in the walking group was an increased 12 minute walk distance. The interval group, however, exhibited significant increases in VO_{2peak} (~30%), peak work (37%), ventilation (20%), respiratory rate (20%), oxygen pulse (19%), ventilatory threshold (~50%), as well as peak inspiratory and expiratory pressures and flow rates. At a 40 watt constant work rate test, only the interval group showed significant increases in tidal volume (20%) and oxygen pulse (17%), and decreases in ventilation (15%), respiratory rate (30%), heart rate (13%), lactate (38%), shortness of breath, and the ventilatory equivalent for oxygen (Gimeniz et al, 2000). Therefore, highly significant adaptations occurred due to interval training, however, these results should be interpreted with caution as the overall study population was younger and less severe than in other studies, and the workload of the continuous training group was not strictly controlled. The adaptations observed cannot likely be generalized to the entire population of patients with COPD, and care should be taken when drawing conclusions regarding the comparison between the two training groups.

Vogiatzis et al. (2002) compared maximal intensity interval training compared with low intensity continuous exercise two days per week over a twelve week period. Thirty six (30 male, 6 female) patients with COPD (FEV_1 = 45% of predicted) were randomized to an interval training group or a continuous training group. The interval training group (n = 18) alternated intervals of 30 seconds at 100% of peak work rate on an incremental test with 30 seconds at rest alternating for a total exercise time of 40 minutes. The continuous training group exercised for 40 minutes at 50%, such that both groups exercised at the same average intensity. A strength of this study was the standardized progression of intensity to 120% of baseline peak work rate at four weeks in the interval group and 60% in the continuous group. At eight weeks, intensities increased to 140%, and 70%, respectively (Vogiatzis et al, 2002). These progressions ensured that the average training intensity remained identical between groups throughout the study.

Interestingly, there were no differences between groups after training. Both groups similarly increased peak work rate (24%), lactate threshold (15%), and work efficiency (11%). Non significant increases were observed in both groups for VO_{2peak} and ventilation. At pre training peak work rate, both groups had similar decreases in VO_2, VCO_2, ventilation, respiratory rate, heart rate, and shortness of breath. An interesting aspect to this study was that they assessed training responses during exercise sessions and found that over a large portion of the twelve weeks, the interval training group exercised with less shortness of breath and a reduced exercise heart rate (Vogiatzis et al, 2002). This may indicate that maximal intensity interval exercise causes less severe symptoms and less central cardiovascular stress. However, this may also be the reason why there was no change in VO_{2peak} or peak ventilation in the interval training group.

Other than the Vogiatzis et al, higher intensity training protocols generally elicit greater physiological adaptation than lower intensity training protocols, however, as there is high variability between studies, specific interpretation is difficult. There is no consensus regarding optimal training protocols at this time. It appears, however, that the protocol selected should reflect the goal of training, and this goal likely should be reflective of the type of exercise limitation observed by an individual patient. The remainder of this review will attempt to synthesize key concepts and generate theoretical discussion related to prescription of exercise intensity.

B.5 Discussion

What is the optimal training intensity for eliciting physiologic benefit in COPD patients?
The question of an optimal training intensity for patients with COPD remains unanswered. Recent evidence, however, has suggested that intensities higher than those often prescribed in rehabilitation programs are not only tolerable, but result in more favorable outcomes. These adaptations to different training intensities, however, must be discussed in the context of defining the limitations to exercise. In order to define an optimal training intensity, we must have a better understanding of why exercise is limited in these patients.

As was suggested earlier, the primary limitation to incremental exercise is not typically a central cardiovascular limitation. Although cardiovascular changes due to COPD alter the exercise responses in patients, they do not appear to be a primary limiting factor (see previous discussion). If the limitations to exercise in these patients are different than those seen in healthy adults, the exercise prescription principles used for healthy adults cannot be used for patients with COPD. Therefore, in order to define optimal training intensities, we must look elsewhere for the defining factors.

The most consistent variable to show a favorable response to high intensity training is work rate. Intuitively, this is not unexpected. The principle of specificity of training dictates that greater gains in a variable will occur when training closely matches that variable (Casaburi, 2001). In the case of high intensity training, because greater work rates are used for training, it is expected that patients will better tolerate higher work rates. However, because these greater increases in work rate are accompanied by lesser or no gains in aerobic capacity, the increases in work rate are, at least in part, independent of aerobic adaptation. This increase in muscular efficiency observed likely indicates that the increases in work rate are more likely due to muscular adaptation (Brooks et al, 2000).

Increases in endurance time are commonly observed and are similar at low and high intensities of exercise training. Increases in endurance time are usually due to delayed lactate production resulting from greater muscular aerobic enzyme activity and muscle oxygenation, which increase VO_2 kinetics and delay the shift to a more anaerobic metabolism (American Thoracic Society, 1999).

Peak ventilation and ventilatory efficiency also increase with training and seem to increase more in higher intensity studies. These increases appear to be the result of a decreased ventilatory demand and, through a delay in the progression of dynamic hyperinflation, an increased ventilatory capacity: the defining characteristics of the classic definition of ventilatory limitation to exercise. Interestingly, many studies label the subjects in the study ventilatory limited prior to exercise training, as well as after. Although ventilatory dysfunction certainly occurs before and after training, increases in peak ventilation suggest that a ventilatory limitation may not always occur. This hypothesis is supported by the fact that factors such as skeletal muscle may play a greater impact on acute exercise capacity (Saey et al, 2003; Casaburi, 2003).

In examining these responses to exercise, and considering what has been discussed related to exercise limitations, it is apparent that the greatest physiological adaptations to training seem to occur in skeletal muscle performance and function, and these adaptation seem to occur most with higher intensity training. Perhaps the definition of an appropriate intensity of exercise requires considering the role of skeletal muscle in determining exercise intolerance, and consequently, abilities to perform daily tasks. There is no doubt, however, that symptoms of dyspnea and fatigue play an important role. Although discussion of dyspnea and fatigue are beyond the scope of this review, it is apparent that similar decreases in symptoms can occur at submaximal training levels in both high and low intensity exercise, and, typically, peak symptoms do not change as the result of either training protocol (Vogiatzis et al, 2002). No matter what exercise intensity is thought to be an 'optimal' intensity, these symptoms must be respected, if not used to define exercise intensity.

How do we determine an appropriate goal of training?

As mentioned, there is no established optimal training intensity for all patients with COPD. The question remains, 'how do we determine an optimal training intensity?' If established guidelines for exercise intensity are not appropriate for these patients, any consideration of optimal prescription must consider the goal of training. As hypothesized above, definition of an optimal intensity appears to require consideration of skeletal muscle adaptation to exercise. The next question to ask is, 'are skeletal muscle adaptations related to the desired outcome of training?' This next section will show how these adaptations may relate to a functional goal of training.

A primary goal of exercise training in pulmonary rehabilitation for patients with COPD has been to increase a patient's ability to sustain tasks of daily living (Casaburi, 1993). As such, methods to increase aerobic capacity through endurance training have been employed. In order to determine optimal intensities for exercise training, however, this goal requires further thought. While it seems reasonable that sustaining tasks is one part of a patient's expectations prior to undergoing exercise training, it is often the more difficult tasks that are described a being most limiting. For example, while a patient may describe becoming short of breath and fatigued while walking, when asked about stair climbing or doing heavy housework, they may reply that they 'can't do that'. Activities of daily living involve both sustained and higher level tasks. Perhaps the inability to perform these higher level tasks is most damaging to a patient's independence. Although increasing the ability to sustain a task is a reasonable expectation from endurance training, should we not expect that the ability to perform, and sustain, higher level tasks is not only desirable, but also achievable? As mentioned, specificity of training dictates that in order to make adequate gains in one type of activity, that activity must be performed at the level of the desired gains. Could, then, a goal of training be to increase a patient's top end ability to perform daily tasks, rather than to sustain lower end activities?

If increasing a patient's ability to sustain tasks is a desired outcome of training, then low intensity endurance training is likely sufficient to produce the desired results. If, however, the desired outcome is to increase a patient's ability to perform tasks that they previously could not perform, then it is appropriate to prescribe higher training intensities. Certainly, higher intensity short term activities play a major role in a patients activities of independent living (Coppoolse et al, 1999). Activities such as sweeping or lifting require a high muscular demand (Levison and Cherniak, 1968). Once performance of the higher level tasks is possible, the ability to sustain these tasks can be addressed.

From a physiological standpoint, shorter term high intensity activity or exercise uses primarily anaerobically driven ATP. This anaerobic energy utilization relies upon the abilities and capacities of skeletal muscle. If rehabilitation is to produce increases in a patient's ability to perform a task anaerobically, training must consist of a component of anaerobic energy system training. In healthy adults, and particularly athletes, anaerobic energy system training is commonly achieved by performing high intensity interval training.

High intensity interval training as an alternative to continuous training

Interval training is defined as repeated short bouts of exercise at intensities higher than that which can be sustained aerobically (Laursen and Jenkins, 2002). Typically, each short bout of exercise (work phase) is followed by a recovery or rest period (rest phase) of defined duration. The purpose of interval training is to repeatedly stress the physiological systems to be used during exercise, sport, or activity at a level at or higher than is required for that activity. Intensity of the work phase dictates the sustainability of that intensity. The higher the work phase intensity, the less time the exercise can be sustained. As well, the work phase will also dictate the duration of the rest phase. This is related to the specific energy system that is primarily active for that intensity and duration. For high intensity interval training, the anaerobic (both phosphocreatine and anaerobic lactic) energy systems are primarily responsible for ATP regeneration. This type of training depends primarily on skeletal muscle metabolic factors (Laursen and Jenkins, 2002).

In athletes and healthy older subjects, interval training has been shown to increase VO_{2max}, endurance capacity, and lactate or ventilatory thresholds, and this increase may actually be greater than the increases due to continuous high intensity training (Poole and Gaesser, 1985; Burke et al, 1994). Certainly, peak work rates are higher after interval training than in continuous training. Interval training also enhances time to fatigue at maximal and supramaximal intensities. Interestingly, despite some controversy, interval training has been shown to increase both anaerobic and aerobic enzyme activity with a corresponding increase in type I fibers and a decrease in type IIb fibers. These changes result in an overall increased oxidative capacity that parallels continuous training, with less central cardiorespiratory stress (Laursen and Jenkins, 2002). Therefore, the potential for greater physiological benefit using interval training has exciting possibilities for clinical populations such as COPD.

There are several reasons that interval training may be more physiologically beneficial in patients with COPD. According to the study by Neder et al (2000), the ventilatory response dynamics constrain exercise tolerance at a critical power. Exercise work rates that are above that critical power cannot be sustained due to rapidly developing dynamic hyperinflation and dyspnea. If the desired goal for a patient is to enhance the ability to perform high level tasks, the only option available to allow such high intensities is intermittent exercise or interval training. As has been shown, interval training in patients with COPD elicits similar benefit, with a reduced ventilatory response (Neder et al, 2000). This reduced ventilatory response delays the onset of dynamic hyperinflation and dyspnea during training (Vogiatzis et al, 2004), allowing a greater opportunity for exercise progression.

Interval training involves periodic respiratory and leg muscle overload that is important for both ventilatory muscle training and leg strength training (Coppoolse et al, 1999). As well, a high level of blood lactate is produced during interval training and that level remains constant throughout an entire exercise bout, indicating an adequate balance between lactate accumulation and removal (Gimeniz et al, 2000). As well, the increased muscle strength that results should assist in enhancing exercise tolerance, endurance, and quality of life (American Thoracic Society, 1999). Reduced symptoms of leg fatigue during exercise after interval training are likely indications of improved strength. For this reason, strength training has also been recommended for these patients (American Thoracic Society, 1999), but is beyond the scope of this review.

Another reason for the use of interval training is to specifically target skeletal muscle metabolism which contributes to exercise limitation in patients with COPD. A metabolic reserve in patients is present during whole body exercise that reduces the ability to adequately supply oxygenated blood to an individual working muscle, when there is significant demand elsewhere (Richardson et al, 1999). The American Thoracic Society and European Respiratory Society (1999) suggest that small muscle groups should be trained so as to minimize the central cardiorespiratory constraints in COPD. They propose that this small muscle activation will prevent the patient from exceeding his ventilatory capacity (American Thoracic Society, 1999). Although this is likely quite true, in order to train all important ambulatory muscles in this fashion, a significant increase in total exercise time is required. Another method of accomplishing a similar goal may be to employ high intensity interval training instead.

Probably the most important reason that interval training may be more beneficial in patients is that it more closely resembles requirements for top end activities of daily living (Coppoolse et al, 1999). The potential to enhance the ability to perform activities of daily living, along with reduced ventilatory demand with training make interval training a highly intriguing option. At this time, however, the limited number of studies prevent the drawing of any concrete conclusions. As well, the studies that have been presented here have limitations that might prevent the generalization and applicability of their results. As mentioned, the study by Gimenez et al (2000) used younger, less severe patients, and did not adequately control the exercise intensity of the comparison group.

It could also be argued that the work phase training intensity in these studies was too low to show adequate benefit. As well, if patients with COPD do not reach their full muscular and metabolic potential during maximal incremental exercise testing (as indicated by a submaximal peak VO_2, and a skeletal muscle metabolic reserve), work rates of 100% of peak probably reflect a lower percentage of their muscular capabilities than would be seen in healthy subjects at 100% of their peak. It is quite possible that patients with COPD would be able to adequately train at work rates higher than the peak achieved during typical clinical exercise testing.

In the study by Vogiatzis et al. (2002), the work phase intensity was 100%, but the rest phase was at 0%, making the overall average work rate much lower (50%). Also, subjects in this study only trained twice per week, which may not be enough for adequate benefit (Laursen and Jenkins, 2002). The study by Coppoolse et al. (1999) had a higher average work rate, but a lower work phase work rate (90%). As well, the subjects in the interval training group performed a combination of both interval training and continuous training, which might alter adaptation (O'Donnell, 2001). The Coppoolse study (1999) also did not progress intensity over the training period, which might minimize the potential gains from their selection of training protocol.

Although with their limitations, these studies have shown that three separate interval training protocols elicit significant training adaptations. In none of these studies, however, was a justification given for the specific protocol used. We are still left with the question, 'how high should intensity be?' As mentioned, it is quite possible that training intensities above baseline peak work rate are tolerable and may elicit greater benefit in patients. To date, however, no research could be found that examined this concept with patients with COPD.

An interesting approach to this concept was suggested by Meyer et al. (1996) who proposed a new method of interval training for patients with chronic heart failure. Her group developed a steep ramp test to assess 'maximal short time exercise capacity' that increased work rate at a much higher rate than a typical incremental test. After a three minute warm up on a cycle ergometer with no load, work rate was increased by 25 watts every 10 seconds to maximum. This test was designed to assess dynamic muscle strength and anaerobic capacity while determining a maximal, unsustained work rate. Interval training intensity was set at 50% of the peak work rate on the steep ramp test, which corresponded to approximately 125% of the peak work rate achieved on a standard incremental test. Interval training was tolerated, and even increased on a weekly basis, for a 30 second work phase and a 60 second recovery phase at 15 watts for 10 repetitions (Meyer et al, 1997).

After training for only three weeks, subjects improved their VO_{2peak} (on a standard incremental test) by close to 20% and their maximum short time exercise capacity by 40% (66 watts). In addition, they found that during interval training, metabolic stress, leg fatigue, dyspnea, and ventilatory equivalents were similar to a level corresponding to a typical training intensity (75% of VO_{2peak}), and cardiac stress was significantly lower than that level. They concluded that, in chronic heart failure patients, this type of exercise testing and training focused on the peripheral muscles, with minimal central strain (Meyer et al, 1997).

Although similar results might not be observed in patients with COPD, this type of testing and interval training do address some of the concerns presented. As well, as skeletal muscle dysfunction presents quite similarly in patients with COPD and those with heart failure (Gosker et al, 2003), a similar response is likely. However, in order to accurately assess the effects of different testing and training protocols, more research is required.

One more key concept to be addressed is that of progression of exercise. Exercise must be progressed in order to elicit more than just immediate improvement (McArdle et al, 2000). With high intensity interval training, progression can occur by increasing work rate, increasing work phase duration, increasing total exercise duration, or decreasing rest phase duration (Laursen and Jenkins, 2002). Optimal progression will likely depend on the overall goal, as discussed previously. If the goal of training is to increase the ability to attain work rates higher than the one at which intensity is currently prescribed, then increasing work rate would be most appropriate. If the training work rates are sufficient to achieve a particular high level of tasks and the goal is to increase the sustainability of that work rate, then both the duration of work and rest phases can be manipulated to achieve the desired effect (Laursen and Jenkins, 2002).

It is also likely, for reasons of optimizing compliance and reducing risk of injury, that interval training should be interspersed with continuous training. The approach taken by Coppoolse and colleagues (1999) is one such method, however it is often common in exercise prescription for athletes to periodize training protocols to obtain the adaptations associated with more than one type of training (Bompa, 1999). For example, after a few weeks of moderate to high intensity continuous exercise, a period of interval training will be introduced for a few weeks, followed by another period of continuous exercise. This approach is quite common and can elicit multidimentional benefits (Bompa, 1999).

Application to clinical practice

The principles discussed in this paper can be applied to a typical pulmonary rehabilitation program, as well as to future research studies examining exercise training in patients with COPD. While insufficient information is available to advance specific guidelines for exercise intensity prescription, it is apparent that higher intensity training will produce greater physiological gains in many patients with COPD. Rehabilitation professionals should be cautioned, however, regarding the specific application of higher intensity training in all patients. It is highly likely, for reasons of safety, and exercise compliance and adherence, that many patients will require lower intensity training, at least initially (American College of Sports Medicine, 2000). Certainly, barring any safety concerns, motivated patients should be able to achieve training intensities well above the common prescription of 'as tolerated'. As is discussed in the section related to current recommendations for training intensity, intensities of 60 – 80% of peak work rate on a standard incremental exercise test can be safely tolerated, with substantial benefit.

The challenge now, for clinicians and researchers alike, is to develop protocols for higher intensity training that are based in strong physiological theory, and will optimize physiological benefit in appropriate patients. The result should be a more specific and strict application of exercise prescription, with the ultimate benefit of achieving higher patient goals and greater benefit.

B.6 CONCLUSION

At present, there are no concrete, specific guidelines for the prescription of exercise intensity for patients with COPD. Because these patients are often limited by factors that normally do not limit the exercise tolerance and capacity of healthy adults, it is difficult to accurately apply the exercise prescription guidelines for healthy adults to patients with COPD. Ventilatory and muscular limitations play a significant role in a patient's ability to exercise.

High intensity exercise training has been shown to elicit greater adaptations in several physiologic systems than those that are elicited in response to lower intensity training. Several options for high intensity training are available, including high intensity continuous training and high intensity interval training, but optimal protocols need to be determined. It is quite possible that the intensity of training normally prescribed in pulmonary rehabilitation and research protocols underestimates the capacity for skeletal muscle adaptation to training. More research is required to assess the efficacy of this possibility, and to elucidate the ultimate effect on patient physiological exercise responses and adaptations, well being, and quality of life.

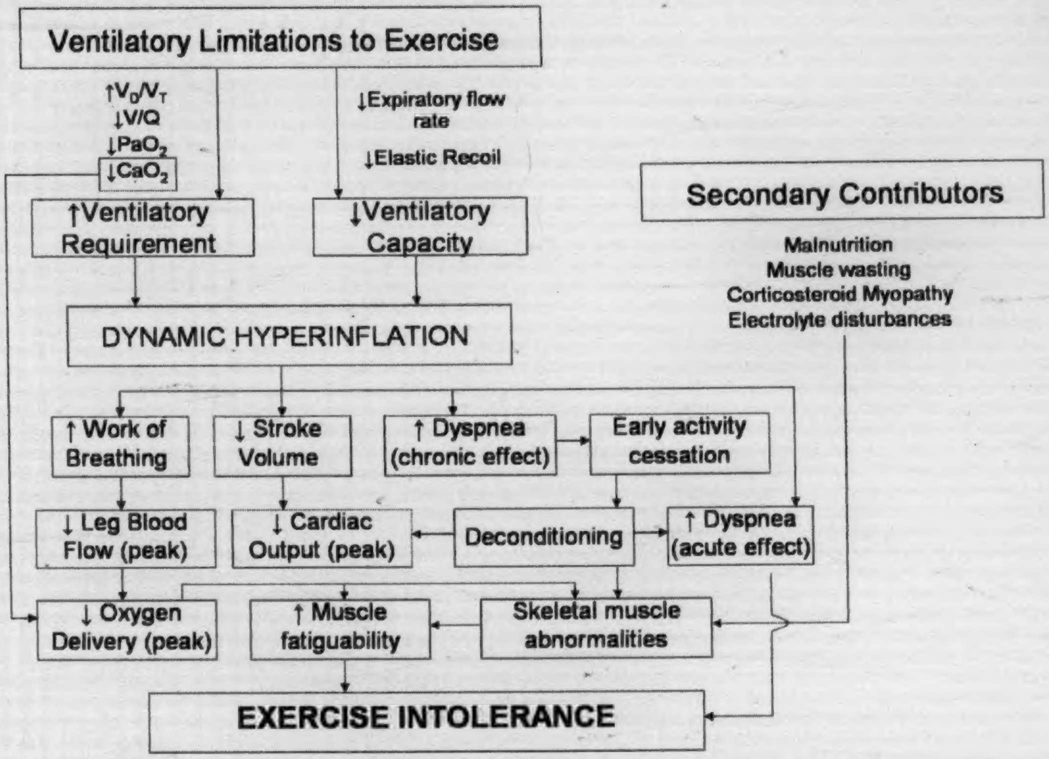
Ventilatory Limitations to Exercise
↑V_D/V_T
↓V/Q
↓PaO_2
↓CaO_2
↓Expiratory flow rate
↓Elastic Recoil
↑Ventilatory Requirement
↓Ventilatory Capacity
Secondary Contributors
Malnutrition
Muscle wasting
Corticosteroid Myopathy
Electrolyte disturbances
DYNAMIC HYPERINFLATION
↑ Work of Breathing
↓ Stroke Volume
↑ Dyspnea (chronic effect)
Early activity cessation
↓ Leg Blood Flow (peak)
↓ Cardiac Output (peak)
Deconditioning
↑ Dyspnea (acute effect)
↓ Oxygen Delivery (peak)
↑ Muscle fatiguability
Skeletal muscle abnormalities
EXERCISE INTOLERANCE

Figure B-1. Proposed schematic diagram of the important mechanisms of exercise intolerance in patients with COPD. The primary limiting factors to exercise and the relative contribution of each factor will vary with each patient. See text for details. Abbreviations: V_D/V_T, dead space volume; V/Q, ventilation perfusion matching; PaO_2, arterial partial pressure of oxygen; CaO_2, arterial oxygen content.

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Appendix C

Additional PhD work

EFFECTS OF LUNG VOLUME CHANGES ON OSCILLATORY FLOW RATE DURING HIGH FREQUENCY CHEST WALL OSCILLATION

(A version of this chapter has been accepted for publication as: Butcher SJ, Pasiorowski MP, Jones RL. Canadian Respiratory Journal, In press, Accepted August, 2006)

C.1 INTRODUCTION

For over 40 years, chest physiotherapy has been used as the primary airway clearance technique in cystic fibrosis (CF) (Wood et al, 1976; Davis et al, 1996; Zach et al, 1990). Unfortunately, skill in application and compliance with prescribed home regimens is often poor due to the time consuming, technically complicated and often uncomfortable nature of the therapy (Passero et al, 1981; Abbot et alo, 1994; Fong et al, 1990). Consequently, newer therapies have been developed in an attempt to provide increased airway clearance, increased independence, enhanced lifestyle, and better compliance with home regimens (Oermann et al, 2001).

High-frequency chest wall oscillation (HFCWO) utilizes a pneumatic vest to compress and oscillate the chest wall and is a relatively new method of facilitating airway clearance. Over the last decade, studies have demonstrated HFCWO to be as effective as standard physiotherapy for patient tolerance (Braggion et al, 1995), hospital stay (Arens et al, 1994), improvement of lung function (Braggion et al, 1995; Arens et al, 1994), and sputum expectoration (Braggion et al, 1995; Arens et al, 1994).

Several studies have characterized the effects of HFCWO on breathing mechanics in humans and animals. HFCWO has been demonstrated to decrease end-expiratory lung volume (EELV) to as much as 50% of the functional residual capacity (FRC) in patients with airway disease (Jones et al, 1995), due to the increased load applied to the chest wall (Zidulka et al, 1983). The decreased EELV was found to have a secondary effect on decreasing the HFCWO-induced oscillated volume in humans (Jones et al, 1995; Dosman et al, 2003) as well as in dogs (Zidula et al, 1983; Gross et al, 1985), but this effect can be reversed with the use of positive expiratory pressure (PEP) in combination with HFCWO. Dosman et al (2003) and Perry et al (1998) found that a small amount of PEP, between 2 and 3.7 cm H_2O, maintains EELV at the level of FRC and it increases mean oscillated volume measured at the mouth in pediatric patients with CF (Dosman et al, 2003) and in older patients with chronic obstructive pulmonary disease (COPD) (Perry et al, 1998). It was concluded that decreases in airway resistance, due to the PEP-induced increased EELV (Guerin et al, 2001), accounted for the increases in oscillated volume. By decreasing airway resistance, PEP also decreases expiratory airflow limitation (Khirani et al, 2001) and it increases collateral airflow in peripheral airways obstructed by secretions (Hofmeyr et al, 1986). The net effect is an increase of oscillatory flow rate (Fosc) during HFCWO. Since increased flow velocity in the airways, where mucous has accumulated, is thought to be responsible for the enhanced mucolytic and mucous clearance effects of HFCWO (Tomkiewicz et al, 1994), PEP may improve these as well. Although previous studies used PEP to increase EELV back to FRC (Dosman et al, 2003; Perry et al, 1998), the optimal EELV during HFCWO may exceed FRC.

In the current investigation, we examined the effects of adding between 2 and 10 cm H_2O continuous positive airway pressure (CPAP) on lung mechanics and Fosc during HFCWO. Because increased levels of CPAP may cause significant patient discomfort, we postulated that an optimal level of CPAP, would occur where the ratio of Fosc to the level of discomfort was highest.

C.2 METHODS

On arrival to the laboratory, subjects performed baseline spirometry using a dry rolling seal spirometer (Sensormedics, Yorba Linda, CA). Subjects then underwent 12 randomized trials of HFCWO (CPAP levels of 0, 2, 4, 6, 8, and 10 cmH_2O at frequencies of 10 and 15 Hz) as described below.

Subjects

This study was approved by the University Of Alberta Health Research Ethics Board and signed informed consent was obtained from each subject. Five healthy subjects (3 males and 2 females) and six patients with obstructive airway disease (4 COPD and 2 CF; 5 males and 1 female) participated in our study (Table C-1). The patients were selected from the outpatient Cystic Fibrosis and Pulmonary Clinics at the University of Alberta Hospital and the normal subjects were undergraduate and graduate students. Spirometry was done prior to beginning the HFCWO protocol. Predicted values for forced vital capacity (FVC) and forced expired volume in one second (FEV_1) were obtained from Morris et al. (19). All patients were clinically stable and taking their usual medications while participating in the study.

Instrumentation

A pneumatic vest system (The Vest^{TM} Airway Clearance System; Hill-Rom; St. Paul, MN) was used to administer HFCWO. The background vest pressure was set at a dial pressure of 4 (a common setting used by patients and which produces a pressure on the chest of approximately 10 cmH_2O without oscillation) and the oscillation frequency was set at either 10 or 15 Hz. The study was conducted with the subjects sitting within a custom-built body plethysmograph in order to measure changes in lung volume. Use of the body plethysmograph was required to obtain inspiratory capacity (IC) since IC measurements made at the mouth during CPAP are technically difficult to obtain. The body plethysmograph (2.13 m high, 1.22 m long, and 0.76 m wide, created an internal volume of approximately 2700 L) was constructed of 1.91 cm thick plywood and 1.27 cm thick Plexiglass. Electromagnets were used to seal the door and permit rapid access to the subject. Several airtight ports in the box wall allowed the connection of breathing tubing and tubing for pressure measurement. Since the subjects inhaled from and exhaled to the room outside the box, the box pressure changes were used to obtain the changes in thoracic displacement, or volume changes during breathing and IC maneuvers. When empty and sealed, the time constants for air leakage were greater than two minutes for both positive and negative box pressure.

When the box was sealed, changes in box pressure were measured by a pressure transducer (Validyne MP45 +/- 50 cmH_2O) and converted to changes in lung volume using a calibration factor. One side of the box pressure transducer was connected to a compensation chamber which was open to the box using a 22 gauge needle. This compensation chamber cancelled any slow box pressure changes, such as those caused by body heat. With subjects in the box and breathing at varying rates and volumes from a spirometer (model 1022, SensorMedics, Yorba Linda, CA) located outside the box, the volume changes measured by the box were highly correlated with those measured by the spirometer ($r = 0.998$, $p<0.001$).

Figure C-1 shows the breathing circuit, which allowed for the physiologic measurements. Subjects breathed room air through a tube connected to a commercial air blower to administer CPAP (Torrington Research, Advanced Respiratory Inc., St. Paul, MN). The expired tubing had a resistance inserted with a lumen of 15 mm to maintain pressure within the breathing circuit. The inspired and expired tubes, the isothermic chamber, and the mouthpiece used by the subject were connected via a four-way PVC connector. Mouth pressure was measured through a port in the PVC connector via a pressure transducer (Validyne MP45 +/- 50 cmH_2O). Another transducer (Validyne MP45 +/- 50 cmH_2O) measured the pressure oscillations in a 20-litre isothermic chamber filled with copper wool which was used to obtain oscillatory volume at the mouth produced by HFCWO. The isothermic chamber was calibrated by rapidly injecting 50 ml of air into the sealed chamber and recording the resultant pressure change. As the mouth and isothermic chamber pressure transducers were located within the body box, the negative ports on both transducers were ducted to the exterior of the box. Oscillatory volume was differentiated to obtain oscillatory flow which was recorded at mid tidal volume expiration over several tidal breaths for all conditions. The oscillated flow was superimposed onto the slower expired tidal flow rate measured with the body box during the same tidal breath to obtain the actual expiratory flow rate, both the fast and slow components. This was then positioned on the volume axis of the standard spirometer-derived flow volume loop using the IC data from the body box (see figure C-5). All pressure, volume, and flow data were recorded digitally (Powerlab 8SP and Chart version 4.2, ADI Instruments Inc) at 200 Hz.

Protocol

Each subject was fitted with an appropriately sized vest, and seated within the body box for 5 minutes following door closure, to allow for temperature equalization. The subject then started the blower on the Vest^{TM} unit, which inflated the vest to a preset dial pressure of 4 (background pressure). The CPAP blower was turned on and adjusted so that mouth pressure during a brief breath-hold was at the desired level of CPAP (0-10 cm H_2O). At 0 cm H_2O CPAP, the blower was turned on to produce a low air flow past the mouth to prevent rebreathing expired air but the resistance in the expired tubing was removed so that mouth pressure remained at atmospheric pressure.

The first two minutes of each trial allowed the subject to become accustomed to the CPAP and to establish a stable EELV. The next 3 minutes combined CPAP with HFCWO, after which the oscillation was stopped, the vest deflated, and the subject cued to complete an IC maneuver. The IC was determined from the level of inspiration above the average EELV obtained from three tidal breaths prior to stopping HFCWO. Subjects scored the perceived comfort of each combination of CPAP and HFCWO on a 100 mm visual analogue scale, ranging from very comfortable (0 mm) to moderately uncomfortable (50 mm) and to unbearable (100 mm). The average values for Fosc were divided by the comfort level for each trial to create an Effectiveness Index.

Analysis

This study was designed to compare oscillatory flow rates and end expiratory lung volumes in patients and control subjects, and Effectiveness Index scores within six levels of CPAP across two oscillation frequencies commonly used by patients. As such a 2 x 6 (Frequency x CPAP level) repeated measures ANOVA was used. When a significant effect was observed, Tukey's post hoc analysis was used to discern where the effect occurred. In order to assess the relationship between oscillatory flow and EELV, a Pearson's r correlation analysis was used.

Alpha was set at 0.05 for all analyses. All analyses examined patients and healthy subjects separately.

C.3 RESULTS

In patients, EELV increased significantly ($p<0.05$) with each level of CPAP regardless of oscillation frequency, with the greatest increases occurring at 15 Hz (Figure C-2). For 10Hz, EELV at 10 cmH_2O CPAP averaged 49.0 %FVC compared to 25.8 %FVC at zero CPAP. For 15 Hz, EELV at 10 cmH_2O CPAP averaged 53.8 %FVC compared to 24.4 %FVC at zero CPAP. In the healthy subjects at 10 Hz, EELV increased to 49.3 %FVC at 10 cmH_2O CPAP from 40.8 %FVC at zero CPAP. Similar values were obtained at 15 Hz.

Oscillated flow rate increased significantly as EELV increased for each frequency in patients ($r = 0.79$, $p<0.05$, Figure C-3). Compared to a CPAP of 0 cmH_2O, Fosc was significantly greater at all CPAP levels for both frequencies ($p<0.05$). As well, the 15Hz condition produced greater Fosc values than the 10Hz condition at CPAP levels of 6, 8, and 10 cmH_2O ($p<0.05$). In contrast, there was not a significant correlation between EELV and Fosc in healthy subjects ($r = 0.125$, $p=0.343$), but, similar to the patients, Fosc was higher at 15 Hz than at 10 Hz at all levels of CPAP.

Our Effectiveness ratio was dependant on Fosc and on the score for discomfort (mm on a 100 mm scale). There were no significant differences between the level of discomfort within either group of subjects for the two oscillation frequencies. The mean discomfort ratings were 22.9 mm vs 17.9 mm at 0 cmH_2O CPAP for the normal subjects and patients, respectively. At 10 cmH_2O CPAP the discomfort ratings were 48.6 mm and 21.8 mm, respectively. Therefore, the patients felt nearly as comfortable at 10 cmH_2O CPAP as they did without CPAP, but the normal subjects felt much more uncomfortable at 10 cmH_2O CPAP than did the patients. There were no significant differences in the Effectiveness index for the two oscillation frequencies and the results for the patient group are shown in figure C-4. The highest level of Effectiveness occurred with 15 Hz at 10 cmH_2O CPAP (26.1 vs. 11.7 $ml \cdot sec^{-1} \cdot mm^{-1}$ at 0 cmH_2O CPAP), due to a systematic increase in Fosc as CPAP increased, without a corresponding increase in level of discomfort.

C.4 DISCUSSION

The novel finding of this research is that increasing EELV above FRC using CPAP during HFCWO significantly increases oscillatory flow rate in patients with chronic airflow obstruction. Also, breathing at lung volumes above FRC does not significantly increase the level of discomfort during HFCWO in the patients we studied. Compared to the study of Perry et al (1998), in which mild levels of PEP were used to return EELV to FRC during HFCWO, our study used higher mouth pressures to increase EELV above FRC with the expectation of further reducing airway resistance and augmenting oscillatory flow rate. Patients, who are expiratory flow limited due to increased airway resistance, responded to CPAP with significantly increased Fosc as end expiratory lung volumes increased. Because breathing at a higher lung volume allows for more flow availability, it is not surprising that Fosc at mid-tidal volume expiration increased with increasing CPAP, as illustrated in Figure C-5. It is likely that CPAP levels higher than 10 cmH_2O would continue to produce increased Fosc since there was no tendency for either EELV or Fosc to level off at 10 cm H_2O CPAP.

The effect of increased Fosc with the addition of CPAP is consistent with previous data (Perry et al, 1998). The results of our study demonstrated that the increase in Fosc from zero CPAP to 10 cmH_2O CPAP was 48% for 10 Hz and 83% for 15 Hz. Dosman et al (2003) found a 14% and increase in oscillatory volume (Vosc) with about 2 cm H_2O PEP in children with cystic fibrosis but those children had near normal airway function when they were studied, thus relatively smaller effects are expected. Using a similar technique as that used by Dosman et al (2003), Perry et al (1998) found a 57% increase in Vosc in severe COPD patients. Given that in vitro studies have shown Fosc to act as a physical mucolytic, enhancing mucous clearance (Tomkiewicz et al, 1994), there is the potential for a clinical benefit of CPAP when added to HFCWO. However, it is important to note that we measured Fosc at the mouth, not at the site of actual mucous accumulation, and we did not measure mucous clearance. As such, we do not know if mucous clearance will be increased with added CPAP. However, others (Hofmeyr et al, 1986) have shown a clinical benefit of PEP, without HFCWO, on mucous clearance. Therefore, increasing lung volume is important clinically and when this benefit is combined with the demonstrated clinical benefit of HFCWO (Braggion et al, 1995; Arens et al, 1994) there is a potential for synergism. Still our demonstration of increased Fosc at the mouth may not translate into increased air flow velocity at the site of mucous accumulation in the periphery, which is thought to be responsible for the important effect of flow in altering mucous rheology (Tomkiewicz et al, 1994). However, it is reasonable to believe that the increased Fosc does in fact represent an increase in flow velocity in the peripheral airways. Figure C-5 shows that our severely obstructed patients were most certainly breathing in the lung volume range where laminar flow occurs (Malo et al, 1975), and laminar flow is proportional to the airway radius to the 4th power. If the radius of a peripheral airway was doubled by CPAP then, at the same alveolar to mouth driving pressure, the flow would increase 16 fold. The cross sectional area in that theoretical airway is proportional to its radius to the 2nd power. The end result of doubling the radius of an airway would be a 4-fold increase in the velocity of flow due mainly to decreasing the airway's resistance. Also, it stands to reason that mucous cannot be cleared from closed airways and CPAP should help to open airways.

In contrast to the patients, no corresponding increase in Fosc was seen in healthy subjects (Figures C-3 and C-4). However, such a result is not surprising, as tidal expiratory flow rate at rest is not flow limited. As well, the healthy subjects did not increase their lung volume with increasing CPAP until the 8 cmH_2O CPAP level (Figure C-3). As the healthy subjects tended to find the testing procedures more uncomfortable than the patients, it is possible that they attempted to maintain EELV by exerting increased expiratory pressure against the CPAP. It is also important to note that Fosc in healthy subjects was greater at all levels of CPAP than in patients but at 10 cmH_2O, Fosc in patients approached the levels observed in the normal subjects. This is an important finding and it relates to the discussion above about Fosc and airflow velocity. The fact that Fosc at the mouth during 10 cmH_2O CPAP was similar between the patients and the normal subjects suggests that air flow velocity in the patients peripheral airways was considerably higher than in the normal subjects since, even at 10 cmH_2O CPAP, the patients most certainly had a much higher airway resistance than the normals (see the flow volume loop in figure C-5). Our findings for normal subjects may have clinical significance too, since HFCWO is used in a variety of mucus clearance disorders, such as in neuromuscular disease (Plioplys et al, 2002) where airway resistance can be normal. Our results suggest that CPAP would be of little or no benefit to these patients.

Furthermore, the level of discomfort from HFCWO did not increase across the levels of CPAP in patients, so higher levels of CPAP ($\leq$10cm H_2O) can be tolerated as well as lower levels, with the potential benefit of increased oscillated flow rate. We evaluated the effects of increased CPAP on oscillatory flow rates during mid expiration since previous work from our laboratory has demonstrated that Fosc during inspiration is less influenced by increased levels of PEP (Dosman et al, 2003; Perry et al, 1998). We think the limitation to oscillatory flow is due to the reduced maximal expiratory flow rate and the flow limitation in patients with airway obstruction.

C.5 CONCLUSIONS

Our study found that, during HFCWO, oscillated flow rate increases with CPAP, and that the addition of CPAP to HFCWO does not significantly decrease patient comfort when compared to HFCWO alone. Therefore, in patients with airway obstruction, the combination of CPAP with HFCWO may add to the effectiveness of HFCWO but this needs to be tested clinically.

Table C-1. Subject demographics

	Patients (n = 6)	Controls (n = 5)
Age (years)	56.7 (16.3)	27.0 (4.9)
Height (cm)	178.8 (7.0)	165.8 (12.3)
Weight (kg)	82.4 (10.9)	66.1 (15.3)
FEV_1 (% pred)	52.8 (23.8)	116.9 (13.9)
FVC (% pred)	78.6 (30.3)	97.6 (10.1)
FEV_1/FVC	0.49 (0.13)	0.95 (0.10)

Data presented as mean (SD). % pred - percent predicted.

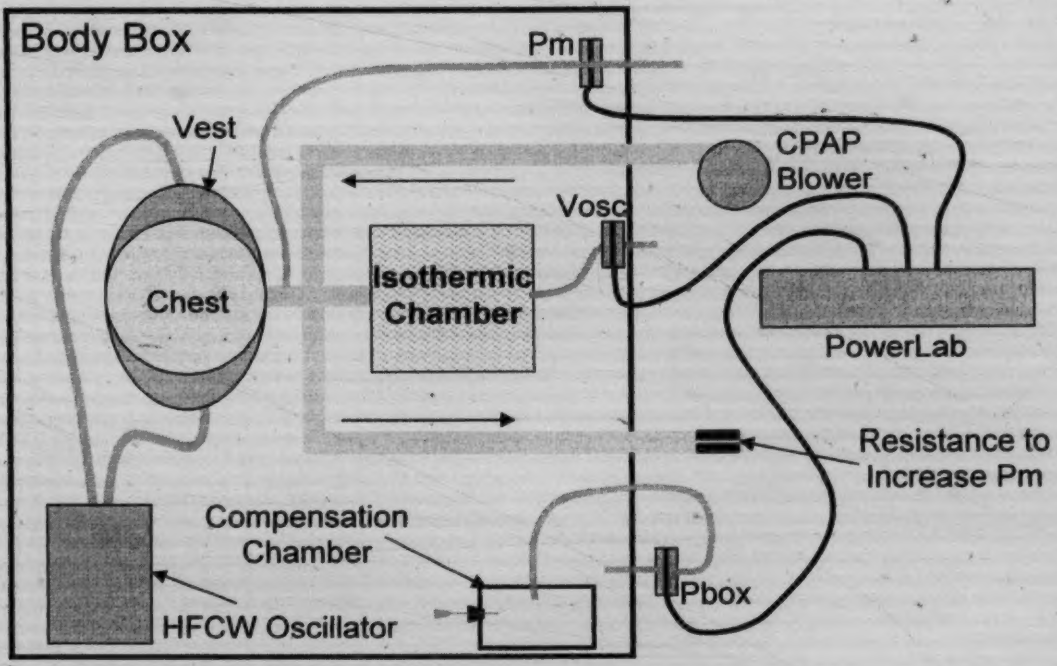
Body Box
Pm
Vest
CPAP
Blower
Vosc
Chest
Isothermic
Chamber
PowerLab
Resistance to
Increase Pm
Compensation
Chamber
Pbox
HFCW Oscillator

Figure C-1. Top diagrammatic view of the experimental set up. Pm = mouth pressure; Vosc = oscillated volume; Pbox = plethysmograph pressure; CPAP = continuous positive airway pressure; PowerLab = the data acquisition system.

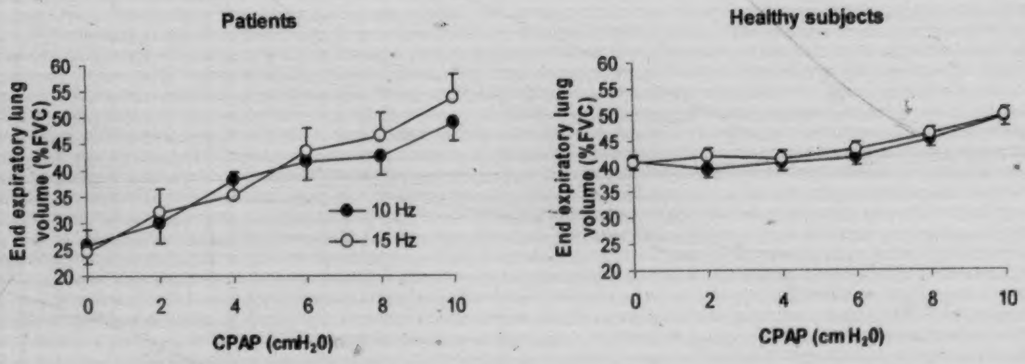

Figure C-2. End-expiratory lung volumes (EELV) at different levels of positive pressure (CPAP) in patients and in healthy subjects at oscillation frequencies of 10 (solid dots) and 15 Hz (open dots). Values expressed as the mean ± SD.

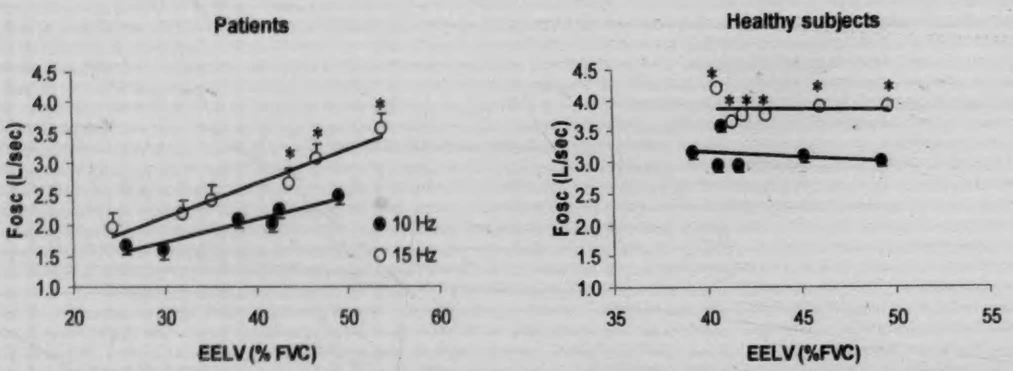

Figure C-3. Oscillatory flow rates (Fosc) plotted against EELV for patients and healthy subjects at oscillation frequencies of 10 (solid dots) and 15 Hz (open dots). Values expressed as the mean ± SD. * = $p < 0.05$ between 15Hz and 10Hz at matched CPAP results. For patients, all levels of CPAP produced greater Fosc than zero CPAP.

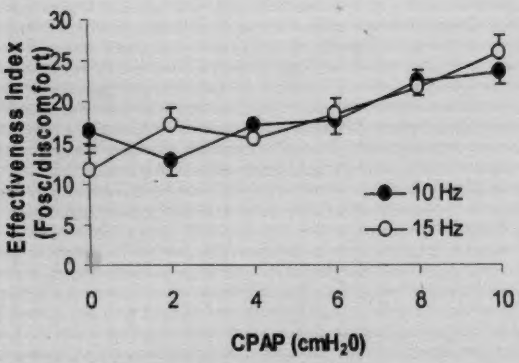

Figure C-4. Effectiveness index scores (oscillatory flow / level of discomfort) for patients. No significant differences were observed between frequencies or across levels of CPAP.

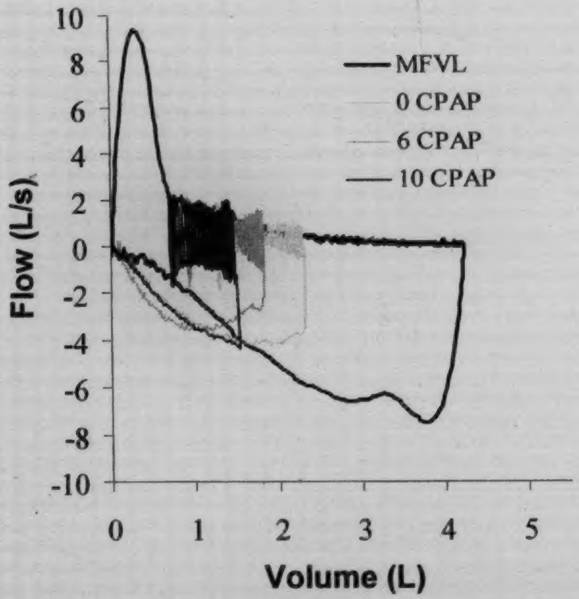

Figure C-5. The expiratory oscillatory flow tracings superimposed upon the tidal expiratory flow volume curve and placed within the maximal flow volume envelope for one cystic fibrosis patient at 0, 6, and 10 cmH_2O CPAP. This figure demonstrates how the increases in lung volume with CPAP increase the oscillatory flow/tidal expiratory flow rates to correspond closely with the available maximal flow rates. The data shown was from a patient at the upper limit for the range of EELV we observed.

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Appendix D

Additional PhD work

THE EFFECTS OF HELIUM-HYPEROXIA ON 6-MINUTE WALKING DISTANCE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

(A version of this chapter has been accepted for publication as: Marciniuk DD, Butcher SJ, Reid JK, MacDonald GF, Clemens R, Jones RL. Chest. In Press, accepted January 2007)

D.1 INTRODUCTION

The characteristic abnormal respiratory mechanics and impaired gas exchange in Chronic Obstructive Pulmonary Disease (COPD) inevitably lead to significant consequences for patients suffering from this disease. COPD patients experience shortness of breath, leading to activity limitation and reduced activity. Therapies aimed at reducing breathlessness and activity limitation, with view to improving health status, are now desirable in management (Celli et al. 2004a; O'Donnell et al. 2004).

Oxygen (O_2) reduces breathlessness, improves exercise (O'Donnell et al. 2001), and increases walking distance (Cukier et al. 2006) in both hypoxemic and non-hypoxemic patients with COPD. Recently, helium (He) in combination with 40% (Eves et al. 2006), 28% (Laude et al. 2006), and 21% O_2 (Palange et al. 2004) was shown to enhance endurance exercise versus room air (RA), and helium-hyperoxia (HeO_2) increased exercise capacity compared to O_2 alone (Eves et al. 2006; Laude et al. 2006). Inspiring HeO_2 during exercise maintains arterial O_2 saturation (SpO_2), reduces ventilatory demand, delays dynamic hyperinflation, and improves respiratory mechanics in COPD patients (Eves et al. 2006). However, while results from the research laboratory are encouraging, the benefit and clinical usefulness of HeO_2 on patient-centered outcomes such as self-paced walking distance has not been explored. Improvements in laboratory testing do not always lead to improvements in walking distance, while improvements in walking do not always correlate with the results from comprehensive exercise testing in patients with chronic cardiopulmonary disease (Barst et al. 2004; Liesker et al. 2002; Barst et al. 2003).

Walking distance can be objectively assessed with the 6-minute walk test (6MWT), which is easy to administer, well tolerated, and reflective of daily living (American Thoracic Society 2002). Importantly, the test is self-paced with patient's choosing a walking speed reflecting the functional activity level important to them (American Thoracic Society 2002). Improvement in the 6MWT would have significant practical implications.

We therefore assessed the effect of altering inspired gas on the 6MWT distance in COPD. We hypothesized that HeO_2 would improve walking distance and reduce shortness of breath compared to both RA and O_2.

D.2 METHODS

Subjects

Sixteen stable COPD subjects (Celli et al. 2004a; O'Donnell et al. 2004), participants in a 3x/week outpatient pulmonary rehabilitation maintenance program, volunteered for the study. All subjects had exertional dyspnea and activity limitation despite their participation. None of the subjects had recent exacerbations (>4 weeks), and continued their usual medications during the study. Subjects receiving supplemental O_2, or with significant cardiovascular or musculoskeletal abnormalities were excluded. The study was approved by research ethics committees, and all subjects provided written informed consent.

Study Design

The study was a blinded, randomized (in blocks of 4 subjects) crossover design requiring 3 visits. Visit 1 consisted of assessing pulmonary function, incremental cardiopulmonary exercise testing (CPET), and a practice 6MWT (each inspiring RA). Exercise tests were separated by a 60 minute rest period. During visits 2 and 3, two 6MWTs were performed on each visit in random order (separated by 60 minutes) to assess the effects of the study gases (see below) on walking distance and symptoms. Testing was undertaken at the same time of day for each subject.

Study Gases

Three different gases mixtures were utilized: RA (21% O_2, 79% N2), O_2 (100% O_2), and HeO_2 (70% He, 30% O_2). All gases were delivered from large capacity cylinders (Medigas, Edmonton, AB) with individually calibrated gas-specific flow meters. Subjects inspired each gas from either a Pulmanex® Hi-Ox® mask (Viasys MedSystems, Wheeling, IL) at a flow of 15 l/min, or from nasal prongs at a flow of 8 l/min ("Nasal O_2" study).

The four arms were: room air with a Hi-Ox® mask (RA), O_2 with a Hi-Ox® mask (Mask O_2), O_2 with nasal prongs (Nasal O_2), and HeO_2 with a Hi-Ox® mask (HeO_2). Subjects were seated and inspired the gas for 5 minutes before each 6MWT. The individual providing instructions and all subjects were blinded to the gas used, and subjects refrained from talking while inspiring the gas prior to walking, during testing, and for 1 minute following the test to avoid detecting any change in voice resonance.

Study Procedures

Spirometry, plethysmographic lung volumes (6200 Autobox, SensorMedics, Yorba Linda, CA), and single-breath diffusing capacity for carbon dioxide (D_Lco) were measured at visit 1. Spirometry and D_Lco were compared to the reported norms of Crapo et al. (1981), lung volumes were compared to Goldman and Becklake (1959).

A symptom-limited CPET on a treadmill was performed while subjects inspired RA. Exercise test measurements included respiratory gas exchange (Vmax229d, SensorMedics, Yorba Linda, CA), intensity of dyspnea and leg fatigue using the modified-Borg scale (Borg 1982), and reason(s) for discontinuing exercise. 6MWTs were performed following accepted guidelines (American Thoracic Society 2002), using a 30 m course. Subjects rested for 10 minutes, and were provided consistent instruction by the same supervisor prior to testing and at each minute of walking. Heart rate, SpO_2, and Borg scores for dyspnea and leg fatigue were measured before and at the end of each 6MWT.

The practice 6MWT (visit 1) was performed breathing RA. On visits 2 and 3, 6MWT were performed while subjects inspired the randomized study gas delivered via 20 meters of tubing from the blinded gas cylinder positioned to the side and at the midpoint of the walking course. The flow meters were calibrated with the tubing in place for each of the gases.

Statistical Analysis

A one-way repeated-measure of analysis of variance (ANOVA) assessed statistical significance (GraphPad Software, San Diego, CA, USA). When the ANOVA detected a significant effect, Bonferroni post-hoc multiple comparison testing was performed. A one-way unpaired t-test was used for post-hoc analysis of O_2 desaturation and ventilatory reserve on walking distance. An alpha of 0.05 was considered significant.

D.3 RESULTS

All subjects recruited completed the study. Subject characteristics are provided in Table D-1. All participants had a significant smoking history (1 current smoker) and a COPD diagnosis established at least 5 years. Baseline function revealed moderate COPD (FEV_1/FVC 48±8% [±SD], mean FEV_1 55±13% predicted) with significant hyperinflation (TLC 130±15% predicted) and gas-trapping (RV 175±37% predicted).

Baseline CPET results are shown in Table D-2. Despite moderate COPD, subjects displayed only mild activity limitation (peak VO_2 82±14% predicted). The majority of subjects reported discontinuing exercise because of shortness of breath. Eight subjects desaturated <90% at end-exercise, 8 subjects had a V_E/MVV (MVV estimated as FEV_1 x 37 (Nici et al. 2006)) of >90% at end-exercise, while 5 subjects demonstrated both. There was no evidence of a learning effect in walking distance during the study (subjects were exercising regularly): subjects walked 494±85 m in the baseline practice 6MWT (visit 1) compared to 497±91 m in the RA 6MWT.

Walking distances in the 6MWT are shown in Figure D-1. Subjects walked significantly farther while breathing HeO_2 (564 m) compared to RA (by 67 m, $p<0.001$) or O_2 (by 44 m Mask O_2, $p<0.001$; by 36 m Nasal O_2, $p<0.001$). Compared to RA, the improvement in walking distance with HeO_2 was greatest in ventilatory-limited subjects (V_E/MVV >90% in the incremental CPET, n=8, 82 m) versus subjects who were not ($V_E/MVV \leq 90\%$, n=8, 51 m), although this trend was not significant (p=0.07). There was no meaningful difference in walking distance response to HeO_2 or to O_2 (both mask and nasal) in subjects who demonstrated significant O_2 desaturation in the initial CPET (end-exercise $SpO_2 \leq 89\%$, n=8) compared to subjects who did not desaturate (end-exercise $SpO_2 \geq 90\%$, n=8).

The reason for stopping each 6MWT, collected from subjects' response to the question: "What, if anything, kept you from walking further?" (American Thoracic Society 2002), is noted in Table D-3. More subjects responded that shortness of breath was the reason in the RA and HeO_2 tests, while both shortness of breath and leg fatigue were more common in the Mask O_2 and Nasal O_2 tests.

Oxygen saturation at the beginning and at the end of each 6MWT is shown in Figure D-2. Subjects demonstrated significant desaturation (Weisman et al. 2003) in the RA (8%, range 1-23%, $p< 0.001$) and Nasal O_2 (5%, range 1-16%, $p<0.001$) tests, which was reduced in the HeO_2 (3%, range 0-8%, p=NS) and Mask O_2 (0%, range 0-1%, p=NS) studies.

There were no significant differences in heart rate at the end of the 6MWT tests (RA 119 ± 13; Mask O_2 110 ± 16, Nasal O_2 110 ± 16, HeO_2 118 ± 19 /min; $p>0.05$).

Group mean modified Borg scores for both shortness of breath and leg fatigue were 0 at the beginning of each walking test. There was a trend towards less shortness of breath at the end of the 6MWT in all studies compared to RA, which reached statistical significance in the Mask O_2 study (Figure D-3). Similarly, despite significantly increased walking distances, there was also a trend towards reduced leg fatigue in all studies compared to RA (end-exercise leg fatigue Borg score for RA 3±2, HeO_2 2±1, Mask O_2 2±1, Nasal O_2 2±1), although this did not reach statistical significance.

The sample size of 16 subjects provides 90% power to detect a 14.8 m change in 6-minute walking distance, acknowledging a SD of the difference between repeated measurements of 17.0 m from our laboratory in this study, $\alpha = 0.05$, and a two-tailed test of significance.

D.4 DISCUSSION

We have demonstrated that moderate COPD subjects significantly increase 6-minute walking distance while inspiring HeO_2 compared to breathing either RA or O_2. Despite the significantly increased walking distance, subjects experience no greater shortness of breath or leg fatigue at the end of the HeO_2 test.

Exercise in COPD has been shown to improve with rehabilitation (Nici et al. 2006), O_2 (Bradley and O'Neill 2005) and bronchodilators (Maltais et al. 2005; O'Donnell et al. 2004), alone or in combinations (Casaburi et al. 2005; Peters et al. 2006). Administering 21% O_2 in He, 40% O_2 in He and O_2 to COPD patients delayed dynamic hyperinflation and optimized respiratory mechanics leading to improved performance, which was dramatic with 40% O_2 in He (Eves et al. 2006). Inspiring 28% O_2 in He has also been shown in COPD to improve exercise in an endurance shuttle walking test (Laude et al. 2006).

In these studies examining the effect of helium with hyperoxia, the practical benefits are difficult to assess. Results from a laboratory utilizing a closed breathing circuit while pedaling on an ergometer (Eves et al. 2006), or a paced test while listening to an audible tone (Laude et al. 2006) may not necessarily equate to a patient's daily activities. In comparison with these maximal tests, the 6MWT is easy to administer, better tolerated, and more reflective of activities of daily living (American Thoracic Society 2002). It is self-paced with the patient choosing their walking speed as they would during their daily lives, reflecting their own functional exercise level (American Thoracic Society 2002). Importantly, the results from the 6MWT have been shown to correlate with notable clinical outcomes in COPD such as mortality, both as part of a composite index (ie. The BODE index (Celli et al. 2004b)), but also as an independent determinant (Martinez et al.

2006). The benefit we have demonstrated in increasing 6MWT distance therefore has significant practical implications for COPD patients.

Our subjects were participants in a maintenance exercise program, and their exercise capacity (see Table D-2) was better than one might predict given the degree of impaired pulmonary function (see Table D-1). In fact because of this, our subjects were functioning as impaired, but highly conditioned individuals. We chose this population to avoid subjects discontinuing exercise solely because of deconditioning or fear of maximal exertion, and therefore provide variable effort. However studying this population could also have limited the magnitude of the response to HeO_2. The mean distance for the HeO_2 test was 564 m, representing a walking speed of ~1.6 m/sec. Walking speed in humans is 1.0-1.4 $m \cdot sec^{-1}$, and the preferred speed for transition from walking to running is 1.88-1.96 m/sec (Thorstensson and Roberthson 1987; Neptune and Sasaki 2005). Instructions for the 6MWT specifically ask subjects to not run or jog (American Thoracic Society 2002). To further increase their walking distance, subjects would not have had much flexibility to increase walking speed and still adhere to the intent of the 6MWT.

A "ceiling" effect on walking distance has also been established in pulmonary vascular disease, a condition where the 6MWT has documented utility (American Thoracic Society 2002). Barst et al. (2004) found this ceiling effect masked efficacy in less severe disease ie. subjects who had a 6MWT distance of >450 m (13/16 subjects had walking distances >450 m in the HeO_2 test in our population). They cautioned this issue must be remembered when interpreting and comparing results from various studies.

We demonstrated that subjects walked farther breathing HeO_2 compared to RA (67 m), Mask O_2 (44 m) or Nasal O_2 (36 m). Improvements of 33–95 m have been reported by others as being significant in lung disease patients, most commonly COPD (American Thoracic Society 2002). Redelmeier et al. (1997) in a study of severe COPD patients (FEV_1 0.98 L) found the distance patients noticed any improvement/worsening was 37–71 m. However while those subjects were also enrolled in a rehabilitation program, their degree of pulmonary impairment was more severe, and the mean 6MWT distance in their study was only 371 m (Redelmeier et al. 1997). As mentioned, comparisons between patients of differing severity are difficult, and as disease severity becomes milder the possibility of a ceiling effect becomes more likely. Finally, interpretation is further complicated because of the lack of optimal reference equations from population-based samples using standardized 6MWT methods (American Thoracic Society 2002).

We administered our gases via tubing with cylinders located centrally in the walking course. Subjects did not carry cylinders to avoid unblinding. In difference to previous work (Laude et al. 2006), but as recommended in guidelines (American Thoracic Society 2002), we did not carry cylinders for the patient. While this may be appropriate for a controlled, paced test (walking to an audible tone), we did not wish to bias subjects, as the 6MWT is intended to be self-paced by the subject.

The improvement in walking distance with HeO_2 was greatest in subjects who were ventilatory limited (V_E/MVV >90%) (Weisman et al. 2003) in the baseline CPET (82 m), although this trend was not significant ($p=0.07$). A larger effect in subjects with greater ventilatory constraint correlates with understanding that He decreases turbulence within larger airways increasing flow rates, decreasing dynamic hyperinflation and dyspnea (Palange et al. 2004). The effect (and benefit) would be greater in subjects with less ventilatory reserve. Since He has a higher viscosity than room air, it is unlikely that the apparent beneficial effect we observed was due to events in the small airways since flow there is laminar and therefore viscosity dependent.

As demonstrated by others (Poulain et al. 2003), SpO_2 at the end of the baseline 6MWT was lower (88%) than at the end of the baseline CPET (89%). However, there was no statistically significant difference in response to HeO_2 compared to RA in subjects who desaturated (end-exercise $SpO_2 \leq 89\%$) compared to subjects who did not (71 m versus 64 m). Subjects received 30% O_2 with the HeO_2 inspirate, reducing the impact of O_2 desaturation (Figure 2). While Eves et al. (2006) used 40% O_2/60% He, it was in a closed-system circuit. The 30% O_2/70% He mixture we used is comparable to the "oxygen28" gas used by Laude et al. (2006), and was sufficient to maintain SpO_2 near the resting value breathing RA (Figure 2). We chose this mixture to provide a hyperoxic gas, but with a higher concentration of He because of the potential for RA dilution with the mask delivery system. We believe the results would have been different if we used a 21% O_2/79% He mixture (Palange et al. 2004), since breathing masks, no matter how efficient, would still dilute the He while not providing supplemental O_2. Although it is likely the gas delivered to the subjects was diluted, the results demonstrate that the actual inspired gas did have a significant effect on our primary outcome variable. Our results suggest however the effects of supplemental O_2 administered via mask or prongs are similar.

We have shown that administering HeO_2 (70% He/30% O_2) to stable outpatients with COPD is both practical and leads to tangible benefits. However, widespread clinical use of HeO_2 would have potential implications. Although the ability to titrate O_2 would be diminished, desaturation was significantly reduced with the HeO_2, and importantly, walking distance was increased. The duration of gas cylinders would be limited with flows of up to 15 $l \cdot min^{-1}$. We did not test HeO_2 at a lower flow, although would predict its effectiveness would be reduced. In addition, while He currently has other medical uses, He cylinders and calibrated flow meters would not be readily available. Moreover, compared to the cost of nasal prongs, the expense of the mask would need to be factored into estimations of cost-effectiveness. Although our study was not designed to assess cost-effectiveness, the practical application and use of HeO_2 in the clinical setting deserves close scrutiny.

A potential benefit of HeO_2 would be in COPD patients in rehabilitation programs. Our subjects increased walking distance, without increased dyspnea or leg fatigue. Using HeO_2 in an exercise program over an extended period might allow increased exercise intensity. While we demonstrated a benefit in our population, further study is required to assess the effects of HeO_2 in subjects not participating in rehabilitation programs. And given prior results which documented an effect of HeO_2 in subjects with severe obstruction (Laude et al. 2006), additional study examining self-paced walking in subjects with more significant disease is warranted.

D.5 CONCLUSIONS

The inhalation of HeO_2 is effective in increasing walking performance and maintaining oxygen saturation in patients with stable COPD compared to breathing room air or 100% oxygen. The increased performance in these patients did not result in more severe symptoms of dyspnea and leg fatigue and may be useful in enhancing exercise performance in a pulmonary rehabilitation setting.

Table D-1. Subject Characteristics and Baseline Pulmonary Function

Gender	9 Female, 7 Male
Age	67 ± 8
Smoking History (pack-years)	42 ± 27
Current Smokers	1
MRC Dyspnea Score	2.1 ± 0.3
BMI	28.2 ± 4.5
FEV_1 (L)	1.42 ± 0.36
FEV_1 (% predicted)	55 ± 13
FVC (L)	2.99 ± 0.74
FVC (% predicted)	89 ± 12
FEV_1/FVC (%)	48 ± 8
TLC (L)	6.70 ± 1.40
TLC (% predicted)	130 ± 15
RV (L)	3.57 ± 0.82
RV (% predicted)	175 ± 37
RV/TLC (%)	53 ± 6
Dlco ($ml \cdot min^{-1} \cdot mm\ Hg^{-1}$)	17.2± 4.1
Dlco (% predicted)	76 ± 16
Resting HR (min^{-1})	84 ± 9
Resting SpO_2 (%)	94.7 ± 1.7

Results are presented as mean ± SD. BMI = body mass index, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, TLC = total lung capacity, RV = residual volume, Dl_{CO} = diffusion capacity of the lung for carbon monoxide, HR = heart rate, SpO_2 = oxygen saturation.

Table D-2. Baseline Incremental Exercise Data

Peak VO_2 $(L \cdot min^{-1})$	1.48 ± .40
Peak VO_2 (% predicted)	82 ± 14
VO_2/kg $(L \cdot min^{-1} \cdot kg^{-1})$	19.7 ± 3.9
Peak V_E $(L \cdot min^{-1})$	49.7 ± 14.0
Peak V_E /MVV (%)	89 ± 18
Peak HR (min^{-1})	130 ± 16
Peak HR (% predicted)	83 ± 9
Desaturation (% from resting)	6 ± 4
End-Exercise SpO_2 (%)	89 ± 5
End-Exercise Modified Borg Score	
SOB	5 ± 2 ("severe")
Leg Fatigue	4 ± 2 ("somewhat severe")
Reason for Stopping Exercise (number of subjects)	SOB = 10 Leg Fatigue = 4 Both = 2

Results are presented as mean ± SD. VO_2 = oxygen consumption, V_E = minute ventilation, MVV = maximal voluntary ventilation, HR = heart rate, SpO_2 = oxygen saturation, SOB = shortness of breath

Table D-3. Reason for Stopping the 6MWT. Post-walk subjects' responses to the question "What, if anything, kept you from walking further?"

	Shortness of Breath	Leg Fatigue	Both
Room Air	10	5	1
Nasal O_2	7	5	4
Mask O_2	7	6	3
HeO_2	11	5	0

Data expressed as the number of subjects (total n = 16).

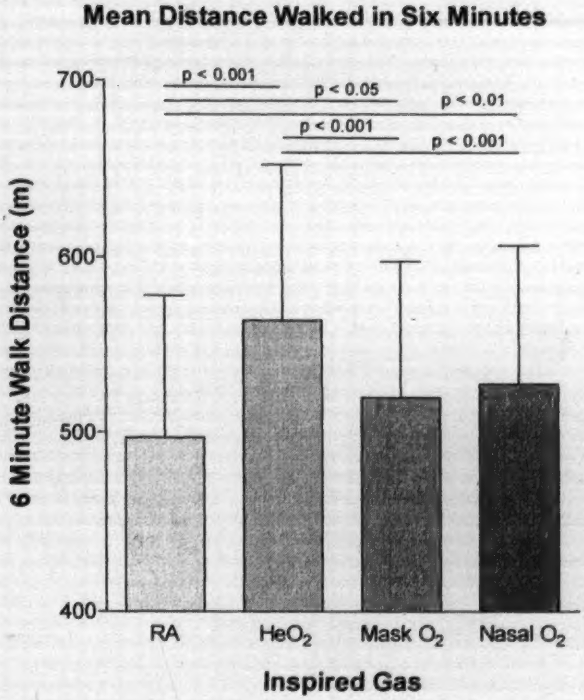

Figure D-1. Group mean 6-minute walking distances for each inspired gas. RA = room air administered via mask, HeO_2 = helium-oxygen administered via mask, Mask O_2 = oxygen administered via mask, Nasal O_2 = oxygen administered via nasal prongs. Results are presented as mean ± SD.

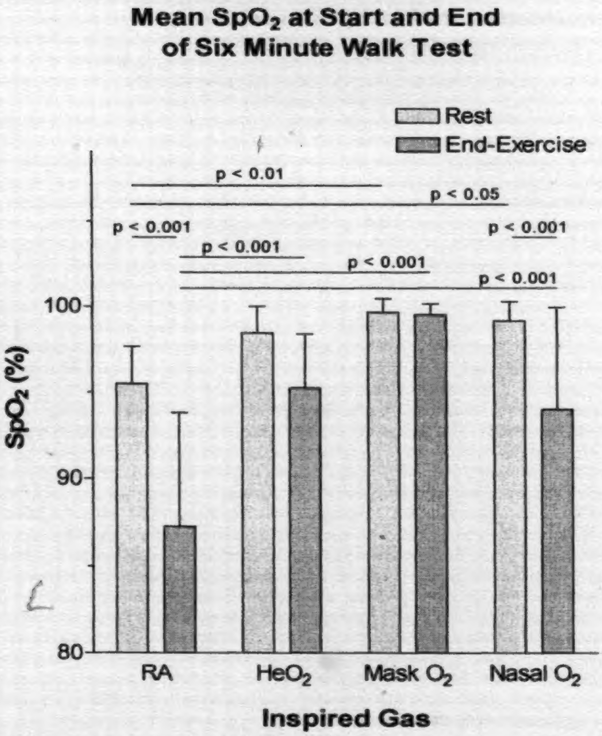

Figure D-2. Group mean oxygen saturations at the start, and at the end of the 6-minute walking tests for each inspired gas. RA = room air administered via mask, HeO_2 = helium-oxygen administered via mask, Mask O_2 = oxygen administered via mask, Nasal O_2 = oxygen administered via nasal prongs. Results are presented as mean ± SD.

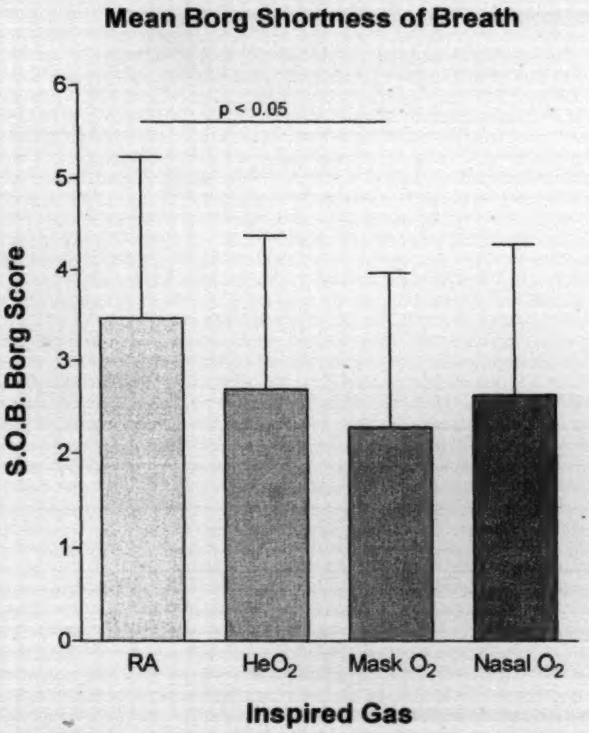

Figure D-3. Group mean shortness of breath Borg scores at the end of 6 minute walk testing for each inspired gas. RA = room air administered via mask, HeO_2 = helium-oxygen administered via mask, Mask O_2 = oxygen administered via mask, Nasal O_2 = oxygen administered via nasal prongs. Results are presented as mean ± SD.

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